(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 March 2009 (19.03.2009)

PCT

(10) International Publication Number
WO 2009/035565 A1

(51) International Patent Classification:
C07C 405/00 (2006.01) *A61P 9/10* (2006.01)
A61K 31/5575 (2006.01) *A61Q 5/00* (2006.01)

(21) International Application Number:
PCT/US2008/010494

(22) International Filing Date:
5 September 2008 (05.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/970,755 7 September 2007 (07.09.2007) US

(71) Applicant *(for all designated States except US)*: **QLT PLUG DELIVERY, INC** [US/US]; 191 Jefferson Drive, Menlo Park, CA 94025 (US).

(71) Applicant and
(72) Inventor: **SHIMIZU, Robert, W.** [US/US]; 26 Danforth Avenue, Laguna Niguel, CA 92677 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **REICH, Cary, J.** [US/US]; 114 Ayala Ct., Los Gatos, CA 95032 (US).

(74) Agents: **STEFFEY, Charles, E.** et al.; Schwegman, Lundberg & Woessner, PA, P.O. Box 2938, Minneapolis, MN 55402 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

WO 2009/035565 A1

(54) **Title:** PROSTAGLANDIN ANALOGUES FOR IMPLANT DEVICES AND METHODS

(57) **Abstract:** The present invention provides prostaglandins, compositions, and methods useful for sustained release of a therapeutic agent over an extended period of time. Exemplary prostaglandins are C_4-C_{32} alkyl esters or amides of prostaglandins, for example, isobutyl esters and amides.

PROSTAGLANDIN ANALOGUES FOR IMPLANT DEVICES AND METHODS

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Application Serial No. 60/970,755, filed September 7, 2007, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

A variety of challenges face patients and physicians in the area of ocular drug delivery. In particular, the repetitive nature of the therapies (multiple injections, instilling multiple eye drop regimens per day), the associated costs, and the lack of patient compliance may significantly impact the efficacy of the therapies available, leading to reduction in vision and many times blindness.

Patient compliance in taking the medications, for example, instilling the eye drops, can be erratic, and in some cases, patients may not follow the directed treatment regime. Lack of compliance can include, failure to instill the drops, ineffective technique (instilling less than required), excessive use of the drops (leading to systemic side effects), and use of non-prescribed drops or failure to follow the treatment regime requiring multiple types of drops. Many of the medications may require the patient to instill them up to 4 times a day.

One promising approach to ocular drug delivery is to place an implant that releases a drug in tissue near the eye. Although this approach can offer some improvement over eye drops, some potential problems of this approach may include implantation of the implant at the desire tissue location, retention of the implant at the desired tissue location, and sustaining release of the drug at the desired therapeutic level for an extended period of time, for example, in the case of glaucoma treatment, undetected and premature loss of an implant can result in no drug being delivered, and the patient can potentially suffer a reduction in vision, possibly even blindness. In some instances, current implant devices may not provide sustained release of uniform amounts of drug each day on a daily

basis for as long as would be ideal, and may require visits to the physician to replace the implant with greater frequency than would be ideal.

Although prostaglandins are pharmaceutically potent in treating eye disorders, for example, lowering the intraocular pressure (IOP), the existing drop administered prostaglandins, for example, latanoprost, bimatoprost, and travoprost may cause irritation and hyperemia to the eye in some patients.

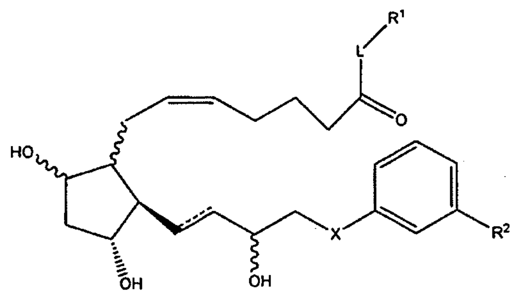
It would be desirable to develop other prostaglandins and provide improved drug delivery.

SUMMARY OF THE INVENTION

The present invention provides prostaglandins, compositions, methods and implant devices for sustained release of a therapeutic agent into the body of a patient, for example, a human or mammal. Although specific reference is made to use in or near the nasolacrimal drainage system, the prostaglandins, as described herein, can be used in other tissue structures in and/or near the eye. Advantageously, the prostaglandins, as described herein, have lower water solubility compared to latanoprost, bimatoprost, and travoprost, and are capable of providing a sustained, efficient and tailored release of a therapeutic agent at the desired therapeutic level for an extended period of time. In some embodiments, lower water solubility of the prostaglandin derivative may provide a more uniform, or zero order, release of the drug each day for an extended period of months.

In some embodiments, the metabolites and/or prodrugs of the prostaglandins, as described herein, may have different penetration and/or partition characteristics, which may influence the clinical endpoints discussed above. The different physical and chemical characteristics of the metabolites and/or prodrugs of the prostaglandins, as described herein, may also afford more latitude in the formulation and loading of medical devices. As such, medical devices various ranges of duration and dosage may be easily fabricated.

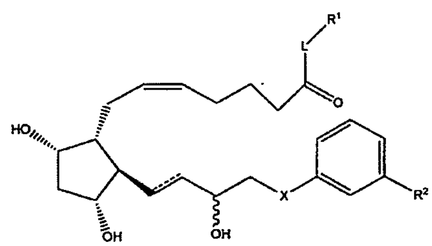
The present invention provides a compound of formula I:



I

and a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof, wherein L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl; R^1 is C_{4-32} alkyl; R^2 is –H or C_1-C_8 haloalkyl; X is -O- or -CH_2-; the dashed bond as represented by ----- represents an optional double bond; and the wavy lines denote that the stereoconfigurations of the carbons to which they are attached can be either R or S. In one aspect the compounds have a water solubility of no more than about 16 mg/ml. In another aspect, the compound has a logarithm of a partition coefficient (logP) greater than about 2.4 at a pH of about 7.4.

The present invention also provides a compound of formula II:



II,

wherein L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

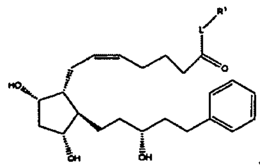
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

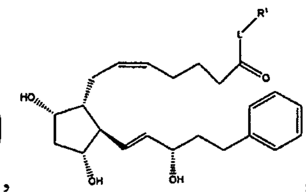
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

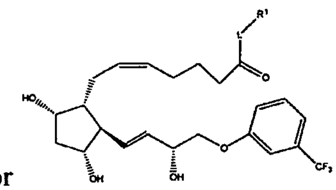
In one embodiment, the compound of formula II is



,



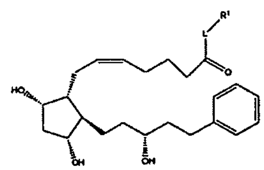
, or



IIa IIb IIc,

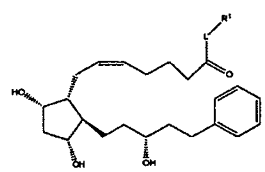
wherein L is -O- or is -NH- and R^1 is isobutyl.

In another embodiment, the compound of the formula II is:



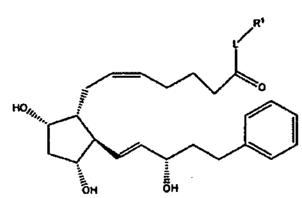
IIa,

wherein L is –O- and R^1 is isobutyl;



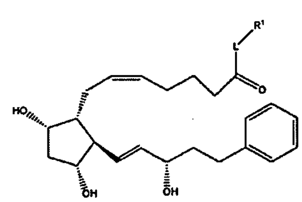
IIa,

wherein L is –NH- and R^1 is isobutyl;



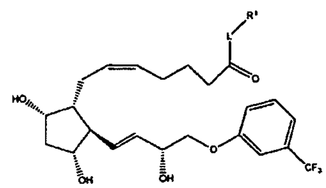
IIb,

wherein L is –O- and R^1 is isobutyl;



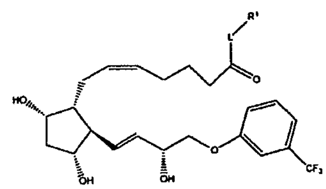
IIb,

wherein L is –NH- and R^1 is isobutyl;



IIc,

wherein L is –O- and R^1 is isobutyl; or



IIc,

wherein L is –NH- and R^1 is isobutyl.

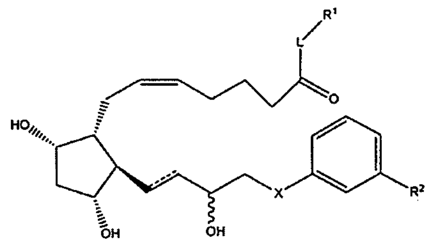
In yet another embodiment, the compound of formula II has a water solubility from about 4 ng/ml to about 16 mg/ml or a logP from about 2.5 to about 9.0 at a pH of about 7.

In one embodiment, the compound of formula II is present in an aqueous humor as a free acid at about 0.5 hours after topical administration to an eye in a mean concentration greater than about 5.7 ng/ml, or at about 1 hour after topical administration in a mean concentration greater than about 18.7 ng/ml, or at about 2 hours after topical administration in a mean concentration greater than about 32.6 ng/ml, or at about 4 hours after topical administration in a mean concentration greater than about 29.0 ng/ml, or at about 24 hours after topical administration in a mean concentration greater than about 0.2 ng/ml, or a combination thereof.

In another embodiment, the compound of formula II is hydrolysable by an esterase.

The present invention further provides a composition including:

a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

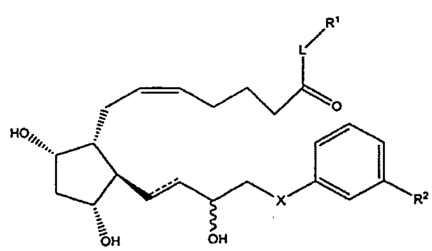
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and a pharmaceutically acceptable carrier.

In one embodiment, the composition is for use in treating an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair. In another embodiment, the eye disease is glaucoma. In yet another embodiment, the pharmaceutically acceptable carrier includes a silicone matrix.

The present invention provides a method of treating glaucoma in a subject in need thereof. The method includes administering to the subject an effective amount of a composition including:

a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

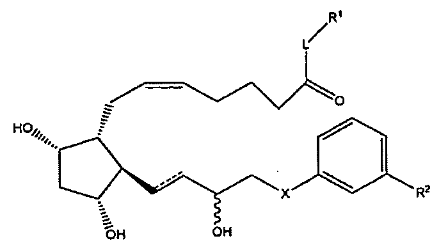
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and

an optional pharmaceutically acceptable carrier.

In one embodiment, the composition is administered to an eye of the subject.

The present invention also provides a method of delivering a therapeutic agent to an eye having associated tears. The method includes: administering the therapeutic agent to the eye in need thereof through operation of a drug core containing the therapeutic agent, wherein the therapeutic agent includes a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is $C_{4\text{-}32}$ alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

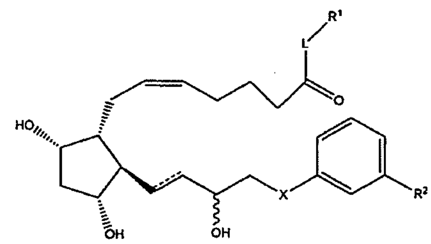
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

In one embodiment, the administering further includes contacting the drug core with the eye and releasing the therapeutic agent to the tears of the eye. In another embodiment, the therapeutic agent and a silicone matrix form a drug core. In yet another embodiment, the drug core is placed in a canaliculus of the eye.

In one embodiment, the therapeutic agent dissolves into the silicone matrix and the silicone matrix remains saturated with the therapeutic agent.

The invention further provides the use of the compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

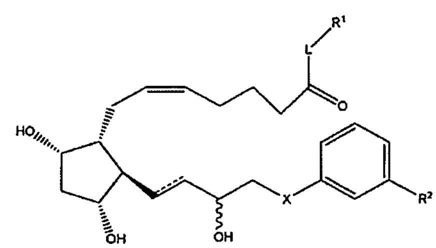
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof, wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4 for medical therapy.

In one embodiment, the medical therapy is the treatment of an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair. In another embodiment, the eye disease is glaucoma.

The invention also provides the use of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

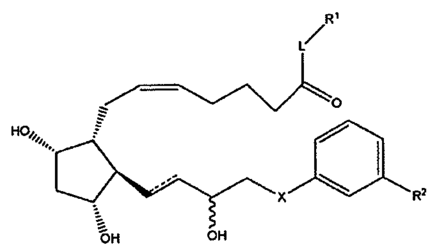
X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; to prepare a medicament for treatment of glaucoma.

In some embodiments, a change in the kinetics of the prostaglandins leaving the cornea may be modulated, for example, by adjusting the rate of cleavage of the metabolites and/or prodrugs of the prostaglandins. For example, the R^1 group may be varied to change the binding constant for the esterase that releases the leaving group to generate the free acid.

The present invention also provides a method of increasing length, thickness, number, or density, of eyelash hair or eyebrow hair. The method includes administering an effective amount of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

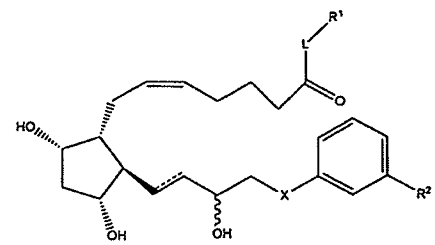
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, to a person on the area where hair growth is desired.

In one embodiment, the effective amount is administered in the form of a liquid composition containing about 0.03% by weight of the compound of formula II is administered to the person. In another embodiment, the liquid composition is administered to an eyelid margin or an eyebrow. In yet another embodiment, the compound of formula II is administered to an eyelid margin or an eyebrow.

To better illustrate the invention described herein, a nonlimiting list of exemplary aspects and embodiments of the invention is provided here:

Aspect 1. A compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

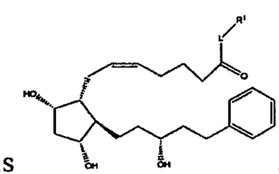
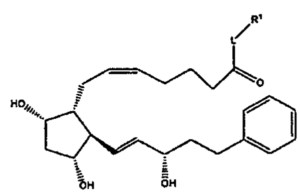
R^1 is C_{4-32} alkyl;

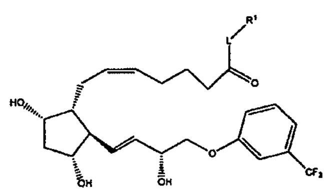
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

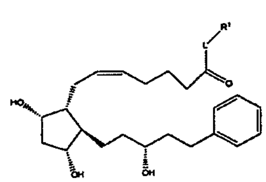
Aspect 2. A compound of Aspect 1, wherein the compound of formula II is , , or



IIa IIb IIc,

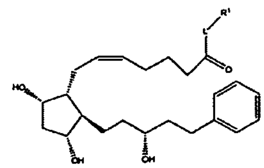
wherein L is -O- or is -NH- and R^1 is isobutyl.

Aspect 3. A compound of any one of Aspects 1-2, wherein the compound of the formula II is:



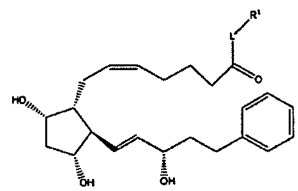
IIa,

wherein L is –O- and R^1 is isobutyl;



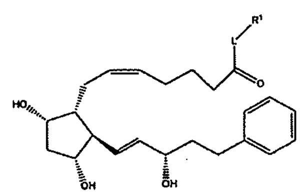
IIa,

wherein L is –NH- and R^1 is isobutyl;



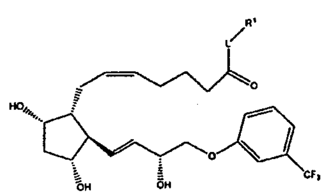
IIb,

wherein L is –O- and R^1 is isobutyl;



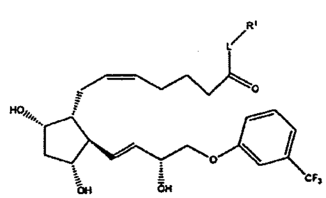
IIb,

wherein L is –NH- and R^1 is isobutyl;



IIc,

wherein L is –O- and R^1 is isobutyl; or



IIc,

wherein L is –NH- and R^1 is isobutyl.

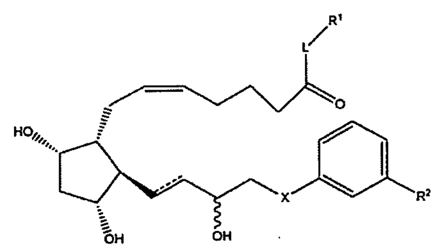
Aspect 4. A compound of any one of Aspects 1-3 having a water solubility from about 4 ng/ml to about 16 mg/ml or a logP from about 2.5 to about 9.0 at a pH of about 7.

Aspect 5. A compound of any one of Aspects 1-4, which is present in an aqueous humor as a free acid at about 0.5 hours after topical administration in a mean concentration greater than about 5.7 ng/ml, or at about 1 hour after topical administration to an eye in a mean concentration greater than about 18.7 ng/ml, or at about 2 hours after topical administration in a mean concentration greater than about 32.6 ng/ml, or at about 4 hours after topical administration in a mean concentration greater than about 29.0 ng/ml, or at about 24 hours after topical administration in a mean concentration greater than about 0.2 ng/ml, or a combination thereof.

Aspect 6. A compound of any one of Aspects 1-5, which is hydrolysable by an esterase.

Aspect 7. A composition comprising:

a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and

a pharmaceutically acceptable carrier.

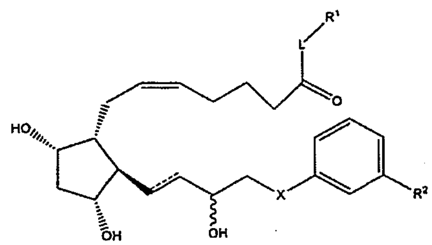
Aspect 8. A composition of Aspect 7, for use in treating an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair.

Aspect 9. A composition of Aspect 8, wherein the eye disease is glaucoma.

Aspect 10. A composition of any one of Aspects 7-9, wherein the pharmaceutically acceptable carrier comprises a silicone matrix.

Aspect 11. A method of treating glaucoma in a subject in need thereof comprising administering to the subject an effective amount of a composition comprising:

a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

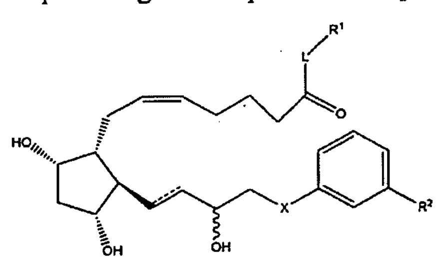
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and

an optional pharmaceutically acceptable carrier.

Aspect 12. A method of Aspect 11, wherein the composition is administered to an eye of the subject.

Aspect 13. A method of delivering a therapeutic agent to an eye having associated tears comprising: administering the therapeutic agent to the eye in need thereof through operation of a drug core containing the therapeutic agent, wherein the therapeutic agent comprises a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

Aspect 14. The method of Aspect 13, wherein the administering further comprises:

contacting the drug core with the eye; and

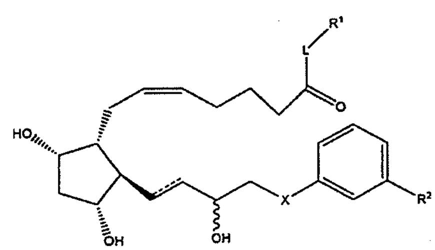
releasing the therapeutic agent to the tears of the eye.

Aspect 15. The method of any one of Aspects 13-14, wherein the therapeutic agent and a silicone matrix form the drug core.

Aspect 16. The method of Aspect 15, wherein the drug core is placed in a canaliculus of the eye.

Aspect 17. The method of any one of Aspects 13-16, wherein the therapeutic agent dissolves into the silicone matrix and the silicone matrix remains saturated with the therapeutic agent.

Aspect 18. A compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

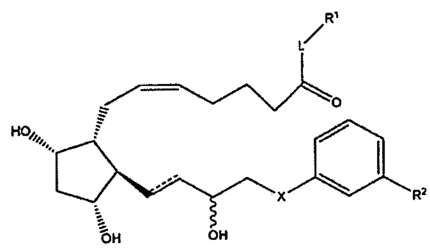
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, for use in medical therapy.

Aspect 19. The use of Aspect 18, wherein the medical therapy is the treatment of an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair.

Aspect 20. The use of Aspect 19, wherein the eye disease is glaucoma.

Aspect 21. Use of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

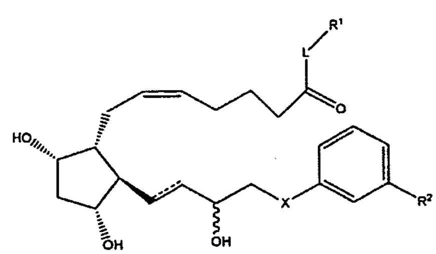
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, to prepare a medicament for treatment of glaucoma.

Aspect 22. A method of increasing length, thickness, number, or density, of eyelash hair or eyebrow hair, comprising administering an effective amount of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, to a person on the area where hair growth is desired.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a method of manufacturing a punctal plug, according to embodiments described herein.

FIG. 2 shows a method of manufacturing a hydrogel rod in accordance with the method of Fig. 1.

FIG. 3 shows a method of molding a silicone plug in accordance with the method of Fig. 1.

FIG. 4 shows a method of assembling the punctal plug component in accordance with the method of in Fig. 1.

FIG. 5 shows a method of manufacturing a drug core insert, in accordance with the method of in Fig. 1.

FIG. 6 shows method 690 of final assembly in accordance with method 600 of Fig. 1.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

Reference will now be made in detail to certain claims of the disclosed subject matter, examples of which are illustrated in the accompanying structures and formulas. While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the disclosed subject matter to those claims. On the contrary, the disclosed subject matter is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the presently disclosed subject matter as defined by the claims.

References in the specification to “one embodiment” indicate that the

embodiment described may include a particular feature, structure, or characteristic, but every embodiment may not necessarily include the particular feature, structure, or characteristic. Moreover, such phrases are not necessarily referring to the same embodiment. Further, when a particular feature, structure, or characteristic is described in connection with an embodiment, it is submitted that it is within the knowledge of one skilled in the art to affect such feature, structure, or characteristic in connection with other embodiments whether or not explicitly described.

Unless otherwise indicated, the words and phrases presented in this document have their ordinary meanings to one of skill in the art. Such ordinary meanings can be obtained by reference to their use in the art and by reference to general and scientific dictionaries, for example, Webster's Third New International Dictionary, Merriam-Webster Inc., Springfield, MA, 1993, The American Heritage Dictionary of the English Language, Houghton Mifflin, Boston MA, 1981, and Hawley's Condensed Chemical Dictionary, 14th edition, Wiley Europe, 2002.

The following explanations of certain terms are meant to be illustrative rather than exhaustive. These terms have their ordinary meanings given by usage in the art and in addition include the following explanations.

As used herein, the term "about" refers to a variation of 10 percent of the value specified, for example, about 50 percent carries a variation from 45 to 55 percent.

As used herein, the term "and/or" refers to any one of the items, any combination of the items, or all of the items with which this term is associated.

As used herein, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

As used herein, the term "administration" refers to a method of placing a device to a desired site. The placing of a device can be by any pharmaceutically accepted means, for example, by swallowing, retaining it within the mouth until the drug has been dispensed, placing it within the buccal cavity, inserting,

implanting, attaching, etc. These and other methods of administration are known in the art.

As used herein, the term "alkyl" refers to a C_1–C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl, ethyl, 1–propyl, 2–propyl, 1–butyl, 2–methyl–1–propyl (iso–butyl, –$CH_2CH(CH_3)_2$), 2–butyl (sec–butyl, –$CH(CH_3)CH_2CH_3$), 2–methyl–2–propyl (tert–butyl, –$C(CH_3)_3$), 1–pentyl, 2–pentyl, 3–pentyl, 2–methyl–2–butyl, 3–methyl–2–butyl, 3–methyl–1–butyl, 2–methyl–1–butyl, 1–hexyl, 2–hexyl, 3–hexyl, 2–methyl–2–pentyl, 3–methyl–2–pentyl, 4–methyl–2–pentyl, 3–methyl–3–pentyl, 2–methyl–3–pentyl, 2,3–dimethyl–2–butyl, 3,3–dimethyl–2–butyl.

The alkyl can be a monovalent hydrocarbon radical, as described and exemplified above, or it can be a divalent hydrocarbon radical (i.e., alkylene).

The alkyl can optionally be substituted with one or more alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. The alkyl can optionally be interrupted with one or more non–peroxide oxy (–O–), thio (–S–), imino (–N(H)–), methylene dioxy (–OCH_2O–), carbonyl (–C(=O)–), carboxy (–C(=O)O–), carbonyldioxy (–OC(=O)O–), carboxylato (–OC(=O)–), imino (C=NH), sulfinyl (SO) or sulfonyl (SO_2). Additionally, the alkyl can optionally be at least partially unsaturated, thereby providing an alkenyl.

As used herein, the term "aqueous medium" refers to a liquid medium composed largely, but not necessarily exclusively, of water. Other components may also be present, for example, salts, co-solvents, buffers, stabilizers, dispersants, colorants, and the like.

As used herein, the term "composition" refers to a product including the specified ingredients in the specified amounts, as well as any product which

results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and deleterious to the recipient thereof.

As used herein, the "compound" refers to a chemical combination of two or more elements that may have an impact on any living system, for example, a cell, nerve or tissue. As also used herein, the term "compound" refers not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active derivatives, including, but not limited to, salts, hydrates, solvates, and the like.

As used herein, the term "derivative" of a compound refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound and /or on an aromatic, alicyclic, or heterocyclic structure, when present. The derivative however is expected to retain the pharmacological activity of the compound from which it is derived.

As used herein, the term "esterase" refers to an enzyme that catalyzes the hydrolysis of an ester. As used herein, the esterase can catalyze the hydrolysis of prostaglandins described herein. In certain instances, the esterase includes an enzyme that can catalyze the hydrolysis of amide bonds of the prostaglandins, for example, a bimatoprost derivative.

As used herein, the term "eye disease" or "eye disorder" refers to physiologic abnormalities of the eye. They may involve the retina, the vitreous humor, lens, cornea, sclera or other portions of the eye, or physiologic abnormalities that adversely affect the eye, for example, inadequate tear production, allergic conjunctivitis, uveitis or corneal transplant.

As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

As used herein, the term "haloalkyl" refers to alkyl as defined herein, substituted by 1–4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3–fluorododecyl, 12,12,12–trifluorododecyl, 2–bromooctyl, 3–bromo–6–chloroheptyl, and the like.

As to any of the groups, as described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any

substitution or substitution patterns, which are sterically impractical and/or synthetically non–feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds, as described herein, are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties, for example, molecular weight, solubility or logP, application properties, for example, activity against the intended target, and practical properties, for example, ease of synthesis.

Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the disclosed subject matter, the total number will be determined as set forth above.

As used herein, the term "mammal" refers to humans, domestic animals (e.g., dogs or cats), farm animals (e.g., cows, horses, or pigs), monkeys, rabbits, mice, and laboratory animals.

As used herein, the term "metabolite" refers to any compound of the formula (I) or formula (II) produced *in vivo* or *in vitro* from the parent drug, or its prodrugs.

As used herein, the term "molecular weight (M.W.)" refers to a weight-average molecular weight, as is well known in the art.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio. Several pharmaceutically acceptable ingredients are known in

the art and official publications, for example, The United States Pharmacopeia describe the analytical criteria to assess the pharmaceutical acceptability of numerous ingredients of interest.

As used herein, the term "pharmaceutically acceptable salts" refers to ionic compounds, wherein a parent non–ionic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues, for example, amines; alkali or organic salts of acidic residues, for example, carboxylic acids; and the like. The pharmaceutically acceptable salts include conventional non–toxic salts and quaternary ammonium salts of the parent compound formed, for example, from non–toxic inorganic or organic acids. Non–toxic salts can include those derived from inorganic acids, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric, nitric, and the like. Salts prepared from organic acids can include those, for example, acetic, 2–acetoxybenzoic, ascorbic, benzenesulfonic, benzoic, citric, ethanesulfonic, ethane disulfonic, formic, fumaric, gentisinic, glucaronic, gluconic, glutamic, glycolic, hydroxymaleic, isethionic, isonicotinic, lactic, maleic, malic, mesylate or methanesulfonic, oxalic, pamoic (1,1'–methylene–bis–(2–hydroxy–3–naphthoate)), pantothenic, phenylacetic, propionic, salicylic, sulfanilic, toluenesulfonic, stearic, succinic, tartaric, bitartaric, and the like. Certain compounds can form pharmaceutically acceptable salts with various amino acids. For a review on pharmaceutically acceptable salts, *see*, e.g., Berge et al., *J. Pharm. Sci.* 1977, *66*(1), 1–19, which is incorporated herein by reference.

The pharmaceutically acceptable salts of the compounds, as described herein, can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of many suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, (1985), 1418, and the disclosure of which is incorporated herein by reference.

As used herein, the term "patient" refers to all mammals, including humans. Examples of patients include, but are not limited to, humans, cows, dogs, cats, goats, sheep, pigs and rabbits.

As used herein, the terms "preferred" and "preferably" refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the invention.

As used herein, the term "prodrug" refers to any pharmaceutically acceptable form of a compound, which upon administration to a patient, provides the compound. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example, hydrolyzed or oxidized, in the host to form a compound of the formula (I) or formula (II). Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs may include, for example, compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound.

As used herein, the term "subject" refers to animals, for example, mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In certain embodiments, the subject is a human.

As used herein, the term "substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, acyloxy, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido,

benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyanato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy. When a substituent is oxo (i.e., =O) or thioxo (i.e., =S) group, then two hydrogens on the atom are replaced.

As used herein, the term "therapeutic agent" refers to any drug, or organic compound, for example, the therapeutic agents may include, for example, agents for treating and/or preventing eye disorders, eye diseases, or the cosmetic enhancement of eyelash hair or eyebrow hair.

As used herein, the term "therapeutic composition" refers to an admixture with an organic or inorganic carrier or excipient, and can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, or other form suitable for use.

As used herein, the term "therapeutically effective amount" is intended to include an amount of a compound, as described herein, or an amount of the combination of compounds, as described herein, e.g., to treat or prevent the disease or disorder, or to treat the symptoms of the disease or disorder, in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.*, 1984, *22*:27, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased activity, or some other beneficial effect of the combination compared with the individual components.

As used herein, the terms "treating" or "treat" or "treatment" refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. As used herein, the term "treatment," covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject,

which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

As used herein, the term "pharmaceutically acceptable excipient" refers to one or more excipients that are useful in preparing a pharmaceutical composition. Excipients are generally safe, non-toxic and neither biologically nor otherwise undesirable, and include excipients that are acceptable for veterinary use as well as human pharmaceutical use.

As used herein, "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar, and "nm" denotes nanometer.

The amides and esters of $PGF_{2\alpha}$, and its analogs are believed to act as prodrugs in the eye, in that the ester or amide form, which is administered is hydrolyzed by endogenous ocular esterase enzymes, releasing the $PGF_{2\alpha}$ analog free acid as the active pharmacologic agent. However, this also releases a potentially toxic and potentially irritant small aliphatic alcohol, for example, isobutanol into the eye. In the case of bimatoprost, ethylamine is released into the eye. While highly effective in reducing intraocular pressure, all of the drugs currently in use; including latanoprost, bimatoprost, travoprost; may cause a significant level of eye irritation in some patients.

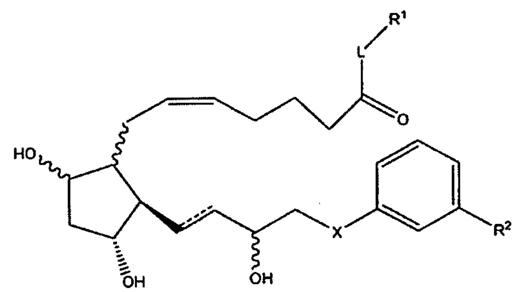
In addition to the foregoing, the isopropyl esters of $PGF_{2\alpha}$ analog compounds, for example, latanoprost and fluprostenol, are highly viscous, glassy oils, which can be difficult to handle and to formulate into ophthalmic solutions. In addition, these compounds can be prone to the retention of potentially toxic process solvents. The higher alkyl esters or amides of $PGF_{2\alpha}$ can be easier to handle and which may not release as irritating of an alcohol or alkylamine upon hydrolysis.

In addition to the irritation caused by the prostaglandins themselves, and particularly the naturally-occurring and synthetic prostaglandins of the type presently on the market, the preservatives typically used in ophthalmic solutions are known to potentially irritate a large percentage of the population. Thus, despite the fact that the prostaglandins represent an important class of potent therapeutic agents for the treatment of glaucoma, the unwanted side effects of

these drugs, particularly ocular irritation and inflammation, may limit patient use and can be related to patient withdrawal from the use of these drugs. The higher alkyl esters and amides of $PGF_{2\alpha}$, as disclosed herein, can be less irritating to patients yet therapeutically effective.

II. Compounds

One embodiment provides a compound of formula I:



I

and a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof. The wavy lines denote that the stereoconfigurations of the carbons to which they are attached can be either R or S.

In formula I, L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl. In one embodiment, -NR^a is -NH.

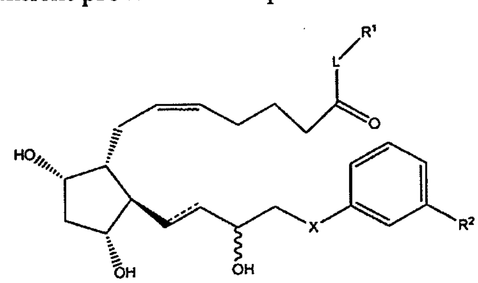
In formula I, R^1 is an alkyl group having greater than 4 carbon atoms. In one embodiment, R^1 is C_4-C_{32} alkyl. In another embodiment, R^1 is C_4-C_{20} alkyl. In one embodiment, R^1 is C_4-C_{12} alkyl. In one embodiment, R^1 is isobutyl.

In formula I, R^2 is -H or C_1-C_8 haloalkyl. In one embodiment, R^2 is -H. In one embodiment, R^2 is -CF_3.

In formula I, X is -O- or -CH_2-. In one embodiment, X is -O-. In one embodiment, X is -CH_2-.

In formula I, the dashed bond as represented by ----- represents an optional double bond.

One embodiment provides a compound of formula II:



II

wherein the substituents R^1, R^2, X, and the dashed bond as represented by ----- represents an optional double bond.

In a group of embodiments of compounds having formula II, L is -O- and X is -O- or $-CH_2$. In one instance, R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$-, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof. In another instance, R^2 is -H or C_1-C_8 haloalkyl, for example, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CCl_3$, and the like.

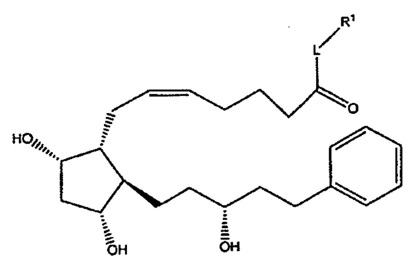
In another group of embodiment, L is $-NR^a$ and X is -O- or $-CH_2$. In one instance, R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof. In another instance, R^2 is -H or C_1-C_8 haloalkyl, for example, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CCl_3$, and the like. In one embodiment, L is -NH.

In one embodiment, the compounds, as described herein, have a low water solubility at 25 °C at a pH between about 7.0 and about 7.2, for example, the compounds have a water solubility of no more than about 0.03% by weight, for example, 0.03, 0.02, 0.01, 0.005, 0.003, 0.002, 0.001 or 0.0001 % by weight. In one embodiment, the compound has a water solubility of no more than about 16 mg/ml. In another embodiment, the compounds have water solubility from about 4 ng/ml to about 16 mg/ml. In another embodiment, the compounds have a water solubility from about 4 ng/ml to about 8 mg/ml. In another embodiment, the compounds have a water solubility from about 4 ng/ml to about 300 μg/ml. In another embodiment, the compounds have a water solubility from about 4 ng/ml to about 50 μg/ml. In yet another embodiment, the compounds have a water solubility from about 4 ng/ml to about 40 μg/ml.

In some embodiments, the compounds have a water solubility less than about a value independently selected from the group consisting of 4,4.1, 4,2, 4,3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71,

72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 135,00, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 20,500, 21,000, 21,500, 22,000, 22,500, 23,000, 23,500, 24,000, 24,500, 25,000, 25,500, 26,000, 26,500, 27,000, 27,500, 28,000, 28,500, 29,000, 29,500, 30,000, 30,500, 31,000, 31,500, 32,000, 32,500, 33,000, 33,500, 34,000, 34,500, 35,000, 35,500, 36,000, 36,500, 37,000, 37,500, 38,000, 38,500, 39,000, 39,500, 40,000, 40,500, 41,000, 41,500, 42,000, 42,500, 43,000, 43,500, 44,000, 44,500, 45,000, 45,500, 46,000, 46,500, 47,000, 47,500, 48,000, 48,500, 49,000, 49,500, 50,000, 60,000, 70,000, 80,000, 90,000, 100,000, 200,000 and 300,000 ng/ml. In certain groups of embodiments, the compounds have a water solubility between about 10 ng/ml to about 50 μg/ml.

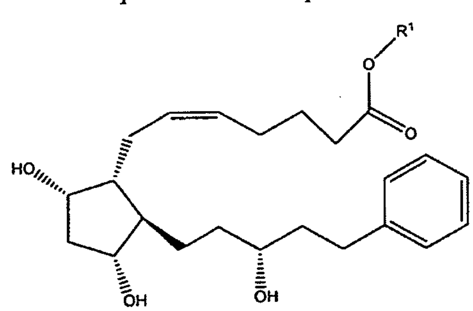
One embodiment provides a compound of formula IIa:



IIa

In certain instances, L is -O- or -NH-. In certain other instances, R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof.

One embodiment provides a compound of formula IIa-1:

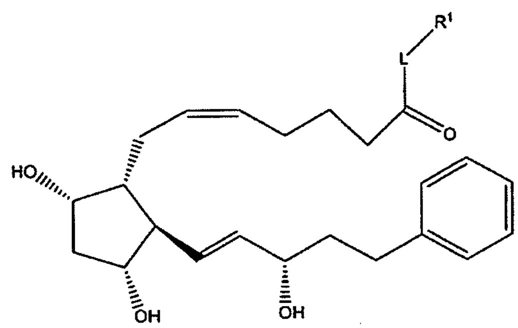


IIa-1

R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof. In one embodiment, R^1 is isobutyl.

In one embodiment, the compounds of formula IIa or IIa-1 have a water solubility of less than about 8 mg/ml. In another embodiment the compounds have a water solubility of about 4 ng/ml to about 8 mg/ml. In another embodiment the compounds have a water solubility of about 4 ng/ml to about 300 μg/ml. In another embodiment the compounds have a water solubility of about 50 μg/ml, or in one embodiment, from about 4 ng/ml to about 10 μg/ml, or in one embodiment, from about 4 ng/ml to about 1 μg/ml, even or in one embodiment, from about 4 ng/ml to about 100 ng/ml, and still even or in one embodiment, from about 4 ng/ml to about 10 ng/ml.

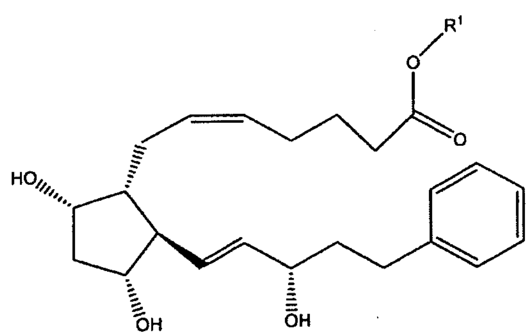
One embodiment provides a compound of formula IIb:



IIb

In certain instances, L is -O- or -NH-. In certain other instances, R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof.

One embodiment provides a compound of formula IIb-1:

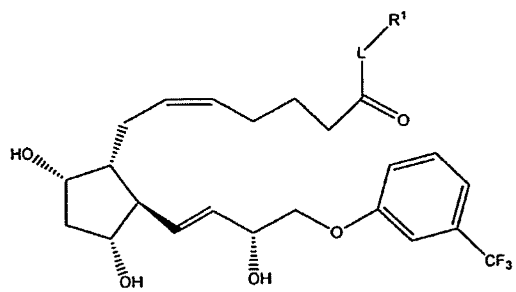


IIb-1

R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof. In one embodiment, R^1 is isobutyl.

In one embodiment, the compounds of formula IIb or IIb-1 have a water solubility from less than about 300 μg /ml. In another about 4 ng/ml to about 40 μg/ml, or in one embodiment, from about 4 ng/ml to about 10 μg/ml, or in one embodiment, from about 4 ng/ml to about 1 μg/ml, even or in one embodiment, from about 4 ng/ml to about 100 ng/ml, and still even or in one embodiment, from about 4 ng/ml to about 10 ng/ml.

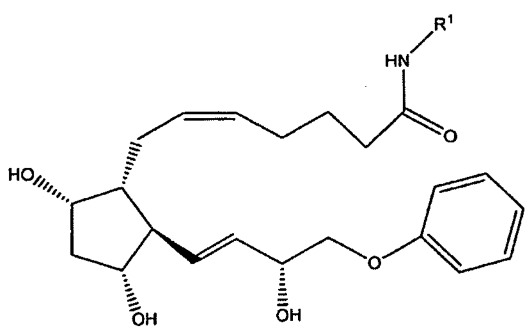
One embodiment provides a compound of formula IIc:



IIc

In certain instances, L is -O- or -NH-. In certain other instances, R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof.

One embodiment provides a compound of formula IIc-1:



IIc-1

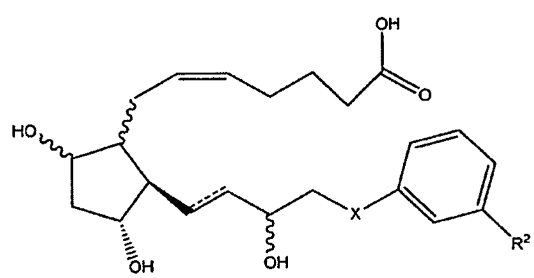
R^1 is C_{4-20} alkyl, for example, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_9H_{19}$, $-C_{10}H_{21}$, $-C_{11}H_{23}$, $-C_{12}H_{25}$, $-C_{13}H_{27}$, $-C_{14}H_{29}$, $-C_{15}H_{31}$, $-C_{16}H_{33}$, $-C_{17}H_{35}$, $-C_{18}H_{37}$, $-C_{19}H_{39}$, or $-C_{20}H_{41}$ and isomers thereof. In one embodiment, R^1 is isobutyl.

In some embodiments, the compounds of formula IIc or IIc-1 have a water solubility from less than about 16 mg/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 8 mg/ml. In

another embodiment, the compounds have a water solubility of about 4 ng/ml to about 300 μg/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 100 μg/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 10 μg/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 1 μg/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 100 ng/ml. In another embodiment, the compounds have a water solubility of about 4 ng/ml to about 10 ng/ml.

In one embodiment, the compound has a logP greater than about 2.4 at a pH of about 7.4. In one embodiment, the compound has a logP at a pH of about 7.4 greater than a value independently selected from the group consisting of: 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, and 9.0.

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active free acid compound. Thus, when a prodrug of Formula I is administered to a mammalian subject, *in vivo*, the ester or amide modifications may be cleaved to release the parent free acid compound of Formula III:



III

wherein the symbols have the same definitions as the formulas above.

In certain embodiments, the compounds are cleavable by an esterase. Esterases naturally present in body tissue, which may cleave the compounds, as described herein, may include, but are not limited to, lipase, for example, carboxylesterase, for example, arylesterase triacylglycerol lipase, phospholipase A2, lysophospholipase, acetylesterase, acetylcholinesterase, cholinesterase, tropinesterase, pectinesterase, sterol esterase, chlorophyllase, L-arabinonolactonase, gluconolactonase, uronolactonase, tannase, retinyl-palmitate

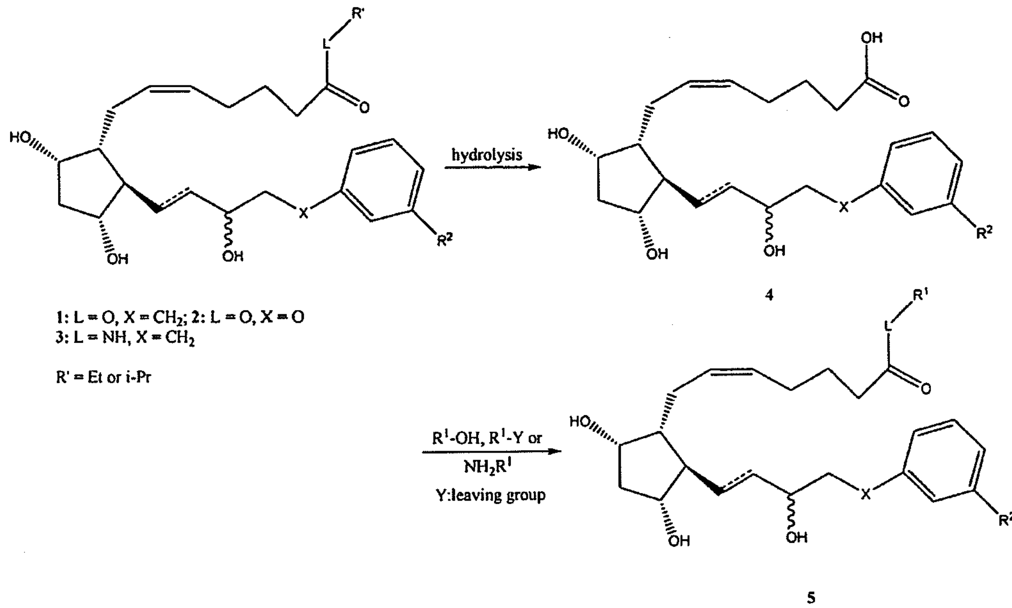
esterase, hydroxybutyrate-dimer hydrolase, acylglycerol lipase, 3-oxoadipate enol-lactonase, 4-lactonase, galactolipase, 4-pyridoxolactonase, acylcarnitine hydrolase, aminoacyl-tRNA hydrolase, D-arabinonolactonase, phosphogluconolactonase, phospholipase A1, 6-acetylglucose deacetylase, lipoprotein lipase, dihydrocoumarin hydrolase, limonin-D-ring-lactonase, steroid-lactonase, triacetate-lactonase, actinomycin lactonase, orsellinate-depside hydrolase, cephalosporin-C deacetylase, chlorogenate hydrolase, a-amino-acid esterase, 4-methyloxaloacetate esterase, carboxymethylenebutenolidase, deoxylimonate A-ring-lactonase, 1-alkyl-2-acetylglycerophosphocholine esterase, fusarinine-C ornithinesterase, sinapine esterase, wax-ester hydrolase, phorbol-diester hydrolase, phosphatidylinositol deacylase, sialate O-acetylesterase, acetoxybutynylbithiophene deacetylase, acetylsalicylate deacetylase, methylumbelliferyl-acetate deacetylase, 2-pyrone-4,6-dicarboxylate lactonase, N-acetylgalactosaminoglycan deacetylase, juvenile-hormone esterase, bis(2-ethylhexyl)phthalate esterase, protein-glutamate methylesterase, 11-cis-retinyl-palmitate hydrolase, all-trans-retinyl-palmitate hydrolase, L-rhamnono-1,4-lactonase, 5-(3,4-diacetoxybut-1-ynyl)-2,2'-bithiophene deacetylase, fatty-acyl-ethyl-ester synthase, xylono-1,4-lactonase, cetraxate benzylesterase, acetylalkylglycerol acetylhydrolase, acetylxylan esterase, feruloyl esterase, cutinase, poly(3-hydroxybutyrate) depolymerase, poly(3-hydroxyoctanoate) depolymerase, acyloxyacyl hydrolase, and polyneuridine-aldehyde esterase.

Preparation of Compounds

Compounds, as described herein, can be prepared using readily available starting materials or known intermediates. Examples of starting materials available from commercial suppliers include, but are not limited to, prostaglandins, for example, latanoprost, travoprost, and bimatoprost, and the free acids of the above compounds; and 2-diethylaminomethyl-4-hydroxy-2-cyclopentenone. Analogs of prodrugs of latanoprost, bimatoprost, and travoprost can be prepared according to the procedures described in Martynow et al., *Euro J. Org. Chem.* 2007, 689-703.

Scheme 1 sets forth an exemplary synthetic scheme for the preparation of compounds, as disclosed herein.

Scheme 1



In Scheme 1, compounds represented by structures **1**, **2** and **3** are hydrolyzed in the presence of a hydrolysis reagent to yield the corresponding carboxylic acid as represented by a common structure **4**. Where appropriate, certain compounds of structure **4** can be obtained from a commercial source. Compounds **4** can subsequently be converted to an ester or an amide of structure **5**. Examples of appropriate reagents and conditions for hydrolysis of an ester include, but are not limited to, TMSCl, Na I, CH_3CN, reflux; and aqueous NaOH, DMF, HCl (*see*, e.g., Martinez et al., *Tetrahedron Lett.*, 1991, *32*, 5931; Khurana et al., *Org. Prep. Proced. Int.*, 1994, *26*, 580). Examples of appropriate reagents and conditions for hydrolysis of an amide include, but are not limited to, $NO^+BF_4^-$ (*see*, e.g., Olah, et al., *J. Org. Chem.*, 1965, *30*, 2386). Examples of reagents for formation of an ester include, but are not limited to, DCC/DMAP and TMSCl (*see*, e.g., Nakao et al., *Bull. Chem. Soc. Jpn.*, 1981, 54, 1267; and Gibson et al., *J. Org. Chem.*, 1994, *59*, 7503). Examples of reagents for amide formation include, but are not limited to, DCC (*see*, e.g., Sheehan et al., *J. Am. Chem.*, 1955, *77*, 1067). The modification and choice of a particular reaction condition is within the capability of an skilled artisan.

The hydrolysis, esterification and amide formation in the reaction pathway set forth in Schemes 1 are applicable to alkyl with any number of carbons, for example, C_4-C_{20} alkyl. The choice of a particular set of reaction

conditions is within the abilities of those of skill in the art (*see*, e.g., March J, Advanced Organic Chemistry, 6th Edition, Wiley, 2007; Sandler SR, Karo W, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., 1986; Wade LG, Compendium of Organic Synthetic Methods, John Wiley and Sons, 1980; and Larock, R. Comprehensive Organic Transformations: A Guide to Functional Group Preparations; 2nd ed., Wiley, 2000). Purification techniques generally known to those skilled in the art include crystallization, distillation, flash chromatography, gas chromatography, size exclusion chromatography, and the like.

Compounds of formula I can be synthesized using the methods disclosed in U.S. Patent Nos. 6,740,772, 6,313,341 and 7,163,959. The choice of protecting groups and leaving groups appropriate for a particular set of reaction conditions is within the abilities of those of skill in the art.

III. Compositions

One embodiment provides compositions including the compounds described herein. In certain embodiments, the composition includes a compound of formula I or II, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In some embodiments, the composition includes compounds of formulas IIa-IIc. In one embodiment, the composition is a pharmaceutical composition for treating an eye disorder or eye disease. Non-limiting exemplary eye disorder or disease treatable with the composition includes age related macular degeneration, alkaline erosive keratoconjunctivitis, allergic conjunctivitis, allergic keratitis, anterior uveitis, Behcet's disease, blepharitis, blood-aqueous barrier disruption, chorioiditis, chronic uveitis, conjunctivitis, contact lens-induced keratoconjunctivitis, corneal abrasion, corneal trauma, corneal ulcer, crystalline retinopathy, cystoid macular edema, dacryocystitis, diabetic keratophathy, diabetic macular edema, diabetic retinopathy, dry eye disease, dry age-related macular degeneration, eosinophilic granuloma, episcleritis, exudative macular edema, Fuchs' Dystrophy, giant cell arteritis, giant papillary conjunctivitis, glaucoma, glaucoma surgery failure, graft rejection, herpes zoster, inflammation after cataract surgery, iridocorneal endothelial syndrome, iritis, keratoconjunctiva sicca, keratoconjunctival inflammatory disease, keratoconus, lattice dystrophy, map-dot-fingerprint

dystrophy, necrotic keratitis, neovascular diseases involving the retina, uveal tract or cornea, for example, neovascular glaucoma, corneal neovascularization, neovascularization resulting following a combined vitrectomy and lensectomy, neovascularization of the optic nerve, and neovascularization due to penetration of the eye or contusive ocular injury, neuroparalytic keratitis, non-infectious uveitisocular herpes, ocular lymphoma, ocular rosacea, ophthalmic infections, ophthalmic pemphigoid, optic neuritis, panuveitis, papillitis, pars planitis, persistent macular edema, phacoanaphylaxis, posterior uveitis, post-operative inflammation, proliferative diabetic retinopathy, proliferative sickle cell retinopathy, proliferative vitreoretinopathy, retinal artery occlusion, retinal detachment, retinal vein occlusion, retinitis pigmentosa, retinopathy of prematurity, rubeosis iritis, scleritis, Stevens-Johnson syndrome, sympathetic ophthalmia, temporal arteritis, thyroid associated ophthalmopathy, uveitis, vernal conjunctivitis, vitamin A insufficiency-induced keratomalacia, vitreitis, and wet age-related macular degeneration. In one embodiment, the pharmaceutically acceptable carrier can include a polymer matrix, for example, a silicone matrix.

The pharmaceutical compositions for the administration of the compounds, as described herein, may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy and drug delivery. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active ingredient is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for topical applications. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-

occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, n-propyl, or p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, for example, sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil, for example, liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin, or cetyl alcohol. Sweetening agents, for example, those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant, for example, ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions, as described herein, may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth, naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

The pharmaceutical compositions, as described herein, may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids, for example, oleic acid find use in the preparation of injectables.

Drug Core

In some embodiments, the pharmaceutical compositions can include a drug core. The drug core includes the therapeutic agent and materials to provide sustained release of the therapeutic agent. The therapeutic agent migrates from the drug core to the target tissue, for example, ciliary body of the eye. The therapeutic agent may optionally be only slightly soluble in the matrix so that a small amount of therapeutic agent is dissolved in the matrix and available for release from the surface of drug core. As the therapeutic agent diffuses from the exposed surface of the core to the tear or tear film, the rate of migration from the core to the tear or tear film can be related to the concentration of therapeutic agent dissolved in the matrix. In addition or in combination, the rate of migration of therapeutic agent from the core to the tear or tear film can be related to properties of the matrix in which the therapeutic agent dissolves. In specific embodiments, the rate of migration from the drug core to the tear or tear film can be based on a silicone formulation. In some embodiments, the concentration of therapeutic agent dissolved in the drug core may be controlled to provide the

desired rate of release of the therapeutic agent. The therapeutic agent included in the core can include liquid, solid, solid gel, solid crystalline, solid amorphous, solid particulate, and/or dissolved forms of the therapeutic agent. In one embodiment, the drug core includes a silicone matrix containing the therapeutic agent. The therapeutic agent may include liquid or solid inclusions dispersed in the silicone matrix. In some embodiments, the metabolites and/or prodrugs of the prostaglandins, as described herein, may allow the prostaglandins to crystallize in the silicone matrix and change to rate of prostaglandin dissolution, elution, and bioavailability.

The drug core can include one or more biocompatible materials capable of providing a sustained release of the therapeutic agent. Although the drug core is described above with respect to an embodiment including a matrix with a substantially non-biodegradable silicone matrix with inclusions of the drug located therein that dissolve, the drug core can include structures that provide sustained release of the therapeutic agent, for example, a biodegradable matrix, a porous drug core, liquid drug cores and solid drug cores. A matrix that contains the therapeutic agent.can be formed from either biodegradable or non-biodegradable polymers. A non-biodegradable drug core can include silicone, acrylates, polyethylenes, polyurethane, polyurethane, hydrogel, polyester (e.g., DACRON from E. I. Du Pont de Nemours and Company, Wilmington, DE, USA), polypropylene, polytetrafluoroethylene (PTFE), expanded PTFE (ePTFE), polyether ether ketone (PEEK), nylon, extruded collagen, polymer foam, silicone rubber, polyethylene terephthalate, ultra high molecular weight polyethylene, polycarbonate urethane, polyurethane, polyimides, stainless steel, nickel-titanium alloy (e.g., Nitinol), titanium, stainless steel, cobalt-chrome alloy (e.g., ELGILOY from Elgin Specialty Metals, Elgin, IL, USA; CONICHROME from Carpenter Metals Corp., Wyomissing, PA, USA). A biodegradable drug core can include one or more biodegradable polymers, for example, protein, hydrogel, polyglycolic acid (PGA), polylactic acid (PLA), poly(L-lactic acid) (PLLA), poly(L-glycolic acid) (PLGA), polyglycolide, poly-L-lactide, poly-D-lactide, poly(amino acids), polydioxanone, polycaprolactone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, polyorthoesters, polyhydroxybutyrate, polyanhydride, polyphosphoester,

poly(alpha-hydroxy acid) and combinations thereof. In some embodiments, the drug core can include at least one of hydrogel polymer.

In specific embodiments, the drug core matrix includes a solid material, for example, silicone, that contains inclusions of the drug. The drug includes molecules, which are very insoluble in water and slightly soluble in the drug core matrix. The inclusions in the drug core can be micro-particles having dimensions from about 1 μm to about 100 μm across. The drug inclusions can include solids and/or droplets of oil, for example, with esters or amides described herein. The drug inclusions can dissolve into the solid drug core matrix and substantially saturate the drug core matrix with the drug, for example, dissolution of prodrug oil into the solid drug core matrix. The prodrug dissolved in the drug core matrix is transported, often by diffusion, from the exposed surface of the drug core into the tear film. As the drug core is substantially saturated with the prodrug, in many embodiments, the rate limiting step of drug delivery is transport of the drug from the surface of the drug core matrix exposed to the tear film. As the drug core matrix is substantially saturated with the drug, gradients in drug concentration within the matrix are minimal and do not contribute significantly to the rate of drug delivery. As surface area of the drug core exposed to the tear film is nearly constant, the rate of drug transport from the drug core into the tear film can be substantially constant.

Work in relation with the present disclosure suggests that the solubility of the therapeutic agent in water and molecular weight of the drug can effect transport of the drug from the solid matrix to the tear. In many embodiments, the therapeutic agent is nearly insoluble in water and has a solubility in water of about 0.03% to about 0.0001% by weight, for example, about 0.03 to about 0.01%, about 0.01 to about 0.002%, about 0.002 to about 0.0005%, about 0.0005 to about 0.0001 % and a molecular weight from about 400 grams/mole to about 1200 grams/mole.

The drug cores may also be modified to utilize carrier vehicles, for example, nanoparticles or microparticles depending on the size of the molecule to be delivered, for example, latent-reactive nanofiber compositions for composites and nanotextured surfaces (Innovative Surface Technologies, LLC, St. Paul, MN, USA), nanostructured porous silicon, known as BioSilicon including micron sized particles, membranes, woven fivers, or micromachined

implant devices (pSividia, Limited, UK) and protein nanocage systems that target selective cells to deliver a drug (Chimeracore, Santa Barbara, CA, USA).

Formulation of therapeutic agent

Compounds of formula I or II are dissolved as a 1% solution in an organic solvent, for example, methyl acetate. An appropriate amount of the 1% solution can be placed in a dish. A stream of dry nitrogen can be used to evaporate the solution until only the compounds remains. The dish with compounds can be placed under vacuum for 30 minutes. In some embodiments, for example, those that are crystalline, for example, bimatoprost derivatives will be used directly as the therapeutic agent, the evaporation and vacuum may not be used to prepare the therapeutic agent. Therapeutic agents containing compounds IIa-c are also prepared using the above methods. Non-limiting examples of compounds of formula IIa-c include isobutyl esters of latanoprost and travoprost and isobutyl amide of bimatoprost.

Preparation of Silicone.

Silicone, for example, NuSil 6385 (NuSil Technology LLC, Carpinteria, CA, USA), can be provided from the manufacturer in a sealed container. An appropriate amount of silicone can be weighed based on the lot size of the build.

Combine therapeutic agent with silicone

The therapeutic agent, for example, prodrugs of formula IIa, for example, the isobutyl ester can be combined with silicone, based on the intended and/or measured percentage of therapeutic agent in the drug core matrix. The percent of compound to silicone can be determined by the total weight of the drug matrix. The therapeutic agent, for example, the compound IIa is incorporated into the silicone by weighing out the appropriate amount of the components. The following formula can be used to determine the percentage of therapeutic agent in the drug core matrix:

Percent Drug = (weight of drug) / (weight of drug + weight of silicone) X 100

The percentage of prodrug in silicone is given by

(20 mg of prodrug) / (20 mg of prodrug + 80 mg of silicone) X 100 = 20%.

IV. Manufacture of Implants

Fig. 1 shows a method 600 of manufacturing an implant according to embodiments described herein. A sub method 610 manufactures a punctal plug. A sub method 650 manufactures a drug core insert, for example, as described above. A sub method 690 assembles the components into an integrated drug delivery system.

Fig. 2 shows a method 620 of manufacturing a hydrogel rod for the punctal plug in accordance with method 600 of Fig. 1. In some embodiments, method 620 includes a sub method, or sub-step, of method 610. A step 622 combines 40% by weight hydrogel with an organic solvent. A step 624 mixes the hydrogel with the solvent. In some embodiments, the hydrogel may dissolve in the organic solvent. A step 626 injects the hydrogel into a silicone tube. In many embodiments, the silicone tube is permeable to the organic solvent. The silicone tube includes a mold to form the hydrogel. A step 628 cures the hydrogel. At least one of a heat or a pressure, in many embodiments, both, can be used to drive off the solvent, for example, through the permeable mold, to cure the hydrogel. A step 629 cuts the cured hydrogel to a desired length. The curing can be optimized with empirical process/validation studies with an adequate a sample size, for example, 10 sample of cured hydrogels, to determine material variability and/or process variability over time. Process variable that can be optimized include time, pressure and temperature of curing. Tolerance analysis associated with the process can also be performed.

Fig. 3 shows a method 630 of molding a silicone plug body 637 in accordance with method 600 of Fig. 1. A step 632 winds a filament including a solid material, for example, a coil 632C, and heat sets the filament. A step 634 places the filament including heat set coil 632C in a mold. A step 636 molds plug body 637 with coil 632C embedded therein. The plug body may include sleeves, tubes, retention structures and/or at least one chamber as described above. The heat setting of the filament can be optimized by appropriately controlling the time and/or temperature of the heat filament based on empirical data from a sample of heat set filaments, for example, 10 filaments. The

molding of the plug at step 636 can be optimized in several ways, for example, appropriate time and temperature, hard tooling of the mold, a multiple cavity mold, and mold equipment parameters

Fig. 4 shows a method 640 of assembling the punctal plug components in accordance with method 600 of in Fig. 1. Step 630 molds the punctal plug body 637 with a coil 632C. Step 620 molds a hydrogel rod. A step 642 inserts the hydrogel rod component into a channel of the plug body component. A step 644 extends windings of coil 632C over the hydrogel rod. A step 648 dip coats the hydrogel rod and plug body. A step 646 may prepare a hydrogel coating solution 646 including, for example, a 5% solution of hydrogel by weight. A needle 648N may be placed in a channel of the plug body to hold the body while the hydrogel rod and plug body are dipped in the solution.

Fig. 5 shows a method 650 of manufacturing a drug core insert, in accordance with method 600 of in Fig. 1. A step 661 prepares a syringe assembly to inject a drug matrix into a polyimide tubing. A step 662 prepares a polyimide tubing for injection. A step 670 prepares a drug core matrix for injection into the tubing. A step 672 injects the drug core matrix into the polyimide tubing. A step 680 cures the matrix inside the polyimide tubing. A step 682 cuts the polyimide tubing and cured matrix to a length and applies an adhesive.

Step 661 can use known commercially available syringes in the syringe assembly. The syringe assembly may include a syringe tube and cartridge assembly. The syringe assembly can be used for injection of the drug core mixture and/or material into the polyimide tubing.

Step 662 can prepare the polyimide tubing for injection by attaching a 15 cm length of polyimide tubing to a luer. The luer can be connected to the syringe for injection of the drug core mixture and/or material. In some embodiments, the tubing connected to the syringe may include PMMA and/or PET. In many embodiments, the tubing includes a material that inhibits release of the therapeutic agent from the drug core through the tubing, for example, a material that is substantially impermeable to the flow of the therapeutic agent through the tubing, such that the flow of therapeutic agent is directed toward the exposed end of the drug core.

Step 670 can prepare a drug core mixture including a therapeutic agent with a matrix material, for example, silicone. In some embodiments, the therapeutic agent may include at least one of compounds of formula IIa-c, for example, isobutyl esters or amides of the free acid forms of latanoprost, bimatoprost, and travoprost. Embodiments can use silicones that include dimethylsiloxane, for example, Med-4011, Med-6385 and Med-6380 (NuSil Technology LLC, Carpinteria, CA, USA).

In a specific embodiment, step 670 can prepare a drug core mixture including inclusions of isobutyl latanoprost ester oil in silicone. The therapeutic agent and drug core matrix material can be prepared prior to mixing the therapeutic agent with the drug core matrix material.

Step 672 can inject the mixture of therapeutic agent and silicone into the tubing. A syringe, for example, a 1 ml syringe, can be connected to the syringe tube and cartridge assembly. A drop of catalyst appropriate for the silicone, for example, MED-6385 curing agent, can be placed into the syringe and the syringe is filled with the uncured mixture of silicone and therapeutic agent, or silicone drug matrix. The polyimide tube is injected with the drug matrix mixture until the tube is filled. The open end of the polyimide tube can be closed off until the silicone begins to solidify.

Step 680 cures the drug core matrix including the mixture silicone and therapeutic agent. The silicone is allowed to cure, for example, for 12 hours. The amount of time and temperature of the cure may be controlled, and empirical data can be generated to determine ideal times and temperatures of the curing. Work in relation with embodiments, as described herein, indicates that the silicone material and drug loading of the core, for example, a percentage of therapeutic agent in the core, may effect the optimal time and temperature of the cure. In some embodiments, empirical data can be generated for each silicone matrix material and percentage of each therapeutic agent to determine an optimal amount of time to cure the injected mixture.

Table 1 shows drug insert silicones that may be used and associated cure properties, according to embodiments described herein. The drug core insert matrix material can include a base polymer including dimethyl siloxane, for example, MED-4011, MED 6385 and MED 6380 (NuSil Technology LLC, Carpinteria, CA, USA). The base polymer can be cured with a cure system, for

example, a platinum-vinyl hydride cure system and/or a tin-alkoxy cure system, both commercially available from NuSil. In many embodiments, the cure system may include a known cure system commercially available for a known material, for example, a known platinum vinyl hydride cure system with known MED-4011. In a specific embodiment shown in Table 1, 90 parts of MED-4011 can be combined with 10 parts of the crosslinker, such that the crosslinker includes 10% of the mixture. A mixture with MED-6385 may include 2.5% of the crosslinker, and mixtures of MED-6380 may include 2.5% or 5% of the crosslinker.

Table 1

Drug Insert Silicone Selections

Material	Base Polymer	Cure System	Crosslinker Percent
MED-4011	Dimethyl siloxane Silica filler material	Platinum vinyl hydride system	10%
MED-6385	Dimethyl siloxane Diatomaceous earth filler material	Tin-Alkoxy	2.5%
MED-6380	Dimethyl siloxane without filler material	Tin-Alkoxy	2.5 to 5 %

Work in relation with embodiments, as described herein, suggests that the cure system and type of silicone material can affect the curing properties of the solid drug core insert, and may potentially effect the yield of therapeutic agent from the drug core matrix material. In specific embodiments, curing of MED-4011 with the platinum vinyl hydride system can be inhibited with high concentrations of prodrug, for example, over 20% prodrug, such that a solid drug core may not be formed. In specific embodiments, curing of MED-6385 and/or

MED 630 with the tin alkoxy system can be slightly inhibited with high concentrations, e.g., 20%, of prodrug. This slight inhibition of curing can be compensated by increasing the time and/or temperature of the curing process, for example, embodiments, as described herein, can make drug cores including 40% prodrug and 60% MED-6385 with the tin alkoxy system using appropriate cure times and temperatures. Similar results can be obtained with the MED-6380 system the tin-alkoxy system and an appropriate curing time and/or temperature. Even with the excellent results for the tin alkoxy cure system, work in relation with embodiments, as described herein, suggests that there may be an upper limit, for example, 50% prodrug or more, at which the tin-alkoxy cure system may not produce a solid drug core. In many embodiments, the therapeutic agent including the prostaglandin analogue, for example, prodrug, in the drug solid drug core may be at least about 5%, for example, a range from about 5% to 50%, and can be from about 20% to about 40% by weight of the drug core.

In some embodiments, the therapeutic agent can include a functional group that can, at least potentially, react with the cure system. In some embodiments, the therapeutic agent can include a prostaglandin analogue, for example, an isobutyl ester or amide of the free acid form of latanoprost, bimatoprost, or travoprost, each of which may include an unsaturated carbon-carbon double bond that can potentially react with the platinum vinyl hydride cure system. These unsaturated carbon-carbon double bonds can be similar to the vinyl group in the platinum cure vinyl hydride system, and can potentially react with the vinyl hydride cure system via a hydrosilation reaction. The isobutyl ester of the free acid form of latanoprost includes an unsaturated carbon-carbon double bond in one of the side chains. The isobutyl amide of the free acid form of bimatoprost and the isobutyl ester of the free acid form of travoprost each include two unsaturated carbon-carbon double bonds, one in each side chain. Work in relation with embodiments, as described herein, indicate that the hydrosilation reaction of the unsaturated double bond in the prostaglandin analogues with in the platinum vinyl hydride cure system does not significantly reduce the quantity of prostaglandin analogue available for release from the drug core.

In some embodiments, the therapeutic agent may include a prostaglandin analogue, which can include hydroxyl groups that can potentially react with the

tin alkoxy cure system. These hydroxyl groups can potentially react with the alkoxy groups via an alkoxy condensation reaction. Esters and amides of latanoprost, bimatoprost, and travoprost each include a molecule with three hydroxyl groups that can potentially react via the alkoxy condensation reaction. Work in relation with embodiments, as described herein, indicate that the alkoxy condensation reaction of the hydroxyl groups in the prostaglandin analogues with in the tin alkoxy cure system does not significantly reduce the quantity of prostaglandin analogue available for release from the drug core.

In some embodiments, the silicone material may include an inert filler to add rigidity to the cured matrix. Work in relation with embodiments, as described herein, suggests that the filler material may increase the rate of release of the therapeutic agent. The MED-4011 and MED-6385 materials are commercially available with the filler material. The MED-4011 material may include an inert silica filler material to add rigidity to the cured silicone matrix. The MED-6385 may include inert diatomaceous earth filler material to add rigidity to the cured silicone matrix.

The inert filler material can increase the concentration of drug in the silicone of the component matrix as the filler material may not substantially absorb the therapeutic agent and the inert filler material can reduce the fraction of silicone in the material drug core matrix. In some embodiments, MED-6385 includes approximately 25% diatomaceous earth filler and approximately 75% dimethyl siloxane. In a specific embodiment, the drug core may include 40% of the therapeutic agent and 60% of the material. The 60% of material, e.g., MED-6385, corresponds to 45% dimethyl siloxane base polymer and 15% inert diatomaceous earth filler. Assuming that very little therapeutic agent is absorbed into the inert filler material, the 40% of therapeutic agent is contained within the 45% of dimethyl siloxane base polymer, such that the concentration of therapeutic agent in the base polymer is 47%, or about 50%. Consequently, the release rate of the therapeutic agent from the exposed surface of the silicone drug core insert can be increased slightly as the concentration of therapeutic agent in the silicone portion of the matrix material can be elevated due to the presence of the filler material.

Step 680 cuts the polyimide tubing with the cured matrix mixture to an intended length and may apply an adhesive to one end of the cut length of tubing.

The polyimide tubing may be inserted into a fixture and cut to a section of the specified length. In some embodiments, the cut sections of polyimide tubing may be placed in a vacuum for 30 minutes. The cut section polyimide tubing including the drug core insert can be inspected and weighed following the vacuum and the weight may be recorded.

An adhesive can be applied to one end of the drug core insert. The adhesive may be applied as a liquid and cured under UV light, for example, cured under UV light for five seconds. In specific embodiments, the adhesive may include Loctite 4305 UV adhesive (Henkel Corporation, Rocky Hill, CT, USA). In many embodiments, the material applied to one end of the drug core insert includes a material that is substantially impermeable to the therapeutic agent such that release of the therapeutic agent through the covered end is inhibited. This inhibition of release from the drug core through the covered end can result in effective and/or efficient delivery of the drug through the exposed surface of the drug core on the opposite end, such that the drug is selectively released to the target tissue and/or bodily fluid, for example, to the tear liquid tear film.

In some embodiments, the exposed end opposite the closed end can be shaped to increase surface area of the exposed end as described above. In some embodiments, a cone with a sharp tip, similar to a sharp pencil tip, can be inserted into the exposed surface to indent the exposed surface with an inverted cone shape that increases surface area. In some embodiments, the exposed end may be crimped to decrease the surface area.

Fig. 6 shows method 690 of final assembly in accordance with method 600 of Fig. 1. A step 692 inserts a drug core component into a channel in the punctal plug. A step 694 packages the punctal plug with the drug core insert in the channel. A step 696 sterilizes the packaged plug and drug core insert. A step 698 releases the product.

Step 692 inserts the drug core into the implant, for example, a punctual plug. The drug core can be inspected prior to insertion and may be part of the step of insertion. The inspection can include visual inspection to ensure that the

sleeve including the cut tubing is completely filled with no voids or foreign particles in the silicone matrix, that the silicone is flush and the same length as the polyimide tube, that the adhesive including cyanoacrylate completely covers one end of the tube, and that the tube is the correct length. The drug insert and implant including the punctual plug can be loaded into a drug insertion tool and holding fixture. The drug insert can be loaded into the implant bore, or channel, using the plunger on the drug insertion tool. The drug insert insertion tool can be removed. The implant including the punctum plug can be inspected to verify that the drug core insert is fully seated in the bore, that the drug core insert is below the surface of the punctual plug flange, and that there is no visible damage to the implant/drug core assembly.

Step 694 packages the punctual plug with the drug core inserted into the channel. The punctual plug may be packaged with known packaging and methods, for example, with an inner pouch, an outer Mylar pouch, a pouch sealer, argon gas, and an inflation needle. In specific embodiments, two completed drug delivery systems, each including the punctual plug implant with drug core insert, are placed in the inner pouch and sealed in the inner pouch. The sealed inner pouch is placed in an outer pouch. The outer pouch may extend about 1/4 beyond a pouch sealer element. The number 25 gauge needle can be inserted into the pouch and under the sealing element with the Argon flowing. The sealer element can be clamped and the package allowed to inflate. The argon flow needle can be removed and the sealing operation repeated. The package can be inspected by pressing gently on the argon filled pouch to check for leaks. If a leak is detected, the inner pouch can be removed and repacked in a new Mylar outer pouch.

Step 696 can sterilize the packaged plug and drug core insert with known sterilization methods, for example, with a commercially available e-beam apparatus (Nutek Corporation of Hayward, CA, USA).

Step 698 can release the product in accordance with final testing and release procedures.

It should be appreciated that the specific steps illustrated in Figs 1 to 6 provide a particular method of manufacturing a plug with a drug core insert, according to some embodiments described herein. Other sequences of steps may also be performed according to alternative embodiments, for example,

alternative embodiments, as described herein, may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in Figs. 1 to 6 may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step. Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

V. Methods of Delivering and Treatment

One embodiment provides a method of treating glaucoma in a subject in need thereof. The method includes administering to the subject an effective amount of compounds of formula I or II or a composition thereof, for example, the compounds are administered to an eye of the subject. In some embodiments, the compounds have formulas IIa-c. In certain embodiments, the compounds are isobutyl esters of the free acid forms of latanoprost or travoprost. In other embodiments, the compounds are isobutyl amides of the free acid form of bimatoprost.

One embodiment provides a method of delivering a therapeutic agent to an eye having an associated tear. The method includes administering the therapeutic agent to the eye in need thereof. In one embodiment, the method includes contacting the therapeutic agent with the eye; and releasing the therapeutic agent to the tear of the eye. In certain instances, the therapeutic agent and a matrix form a drug core. In certain other instances, the therapeutic agent is placed in a canaliculus of the eye. The therapeutic agent can dissolve into the matrix and the matrix remains substantially saturated with the therapeutic agent. The therapeutic agents includes compounds of formulas I, II, or IIa-c. Non-limiting examples of compounds include isobutyl esters and amides of the free acid form of latanoprost, bimatoprost, and travoprost.

The amount of drug associated with the drug-delivery device may vary depending on the particular agent, the desired therapeutic benefit and the time during which the device is intended to deliver the therapy. Since the devices, as described herein, present a variety of shapes, sizes and delivery mechanisms, the amount of drug associated with the device will depend on the particular disease or condition to be treated, and the dosage and duration that is desired to achieve the therapeutic effect. Generally, the amount of drug is at least the amount of

drug that upon release from the device, is effective to achieve the desired physiological or pharmacological local or systemic effects.

Embodiments of the drug delivery devices, as described herein, can be adapted to provide delivery of drug at a daily rate that is substantially below the therapeutically effective drop form of treatment so as to provide a large therapeutic range with a wide safety margin, for example, many embodiments treat the eye with therapeutic levels for extended periods that are no more than 5 or 10 per cent of the daily drop dosage. Consequently, during an initial bolus or washout period of about one to three days, the implant can elute the therapeutic agent at a rate that is substantially higher than the sustained release levels and well below the daily drop form dosage, for example, with an average sustained release level of 100 ng per day, and an initial release rate of 1000 to 1500 ng per day, the amount of drug initially released is less than the 2500 ng of drug that may be present in a drop of drug delivered to the eye. This use of sustained release levels substantially below the amount of drug in a drop and/or drops administered daily allows the device to release a therapeutically beneficial amount of drug to achieve the desired therapeutic benefit with a wide safety margin, while avoiding an inadequate or excessive amount of drug at the intended site or region.

An extended period of time may mean a relatively short period of time, for example, minutes or hours (for example, with the use of an anesthetic), through days or weeks (for example, the use of pre-surgical or post-surgical antibiotics, steroids, NSAIDs, and the like), or longer (for example, in the case of glaucoma treatments), for example, months or years (on a recurring basis of use of the device).

A drop of Xalatan (Pfizer, Groton CT, USA) contains about 2.5 μg of latanoprost, assuming a 50 μL drop volume. Therefore, assuming that about 8% of 2.5 μg is present 5 minutes after instillation, only about 200 ng of drug remains on the eye. Based on the latanoprost clinical trials, this amount is effective in lowering IOP for at least 24 hours. Pfizer/Pharmacia conducted several dose-response studies in support of the NDA for Xalatan. The doses ranged from 12.5 μg/mL to 115 μg/mL of latanoprost. The current dose of latanoprost, 50 μg/mL, given once per day, was shown to be optimal. However, even the lowest doses of 12.5 μg/mL QD or 15 μg/mL BID consistently gave

about 60-75% of the IOP reduction of the 50 μg/mL QD dose. Based on the assumptions above, a 12.5 μg/mL concentration provides 0.625 μg of latanoprost in a 50 μL drop, which results in only about 50 ng (8%) of drug remaining in the eye after 5 minutes.

In many embodiments, the concentrations of compounds of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides (formula IIa) are about 0.0001%, 0.001%, 0.01%, 0.1%, or 1 percent, that of latanoprost, and in specific embodiments, the concentrations of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides may be about 1/10,000th, 1/1000th, 1/500th, 1/100th, 1/50th, or 2 percent, that of latanoprost, for example, commercially available solution preparations of latanoprost are available at concentrations 0.005%, often delivered with one drop per day. The 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides, as described herein, allow the delivery of one drop every 2, 3, 4, or 5 days. In many embodiments, the therapeutically effective concentration of drug released from the device per day can be about 1/10,000th, 1/1000th, 1/500th, 1/100th of latanoprost, about 4, 5, 6, 7, 8, 9 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30 to 150 ng per day, for example, about 80 ng, assuming tear washout and bioavailability similar to latanoprost, for example, the amount of drug on the implantable device, can be significantly less- approximately 0.0001%-0.001%, 0.001%-0.01%, 0.01 %-0.1% or 1 % to 2% of latanoprost, bimatoprost or travoprost, for example, about 2.7 to 13.5 μg, and can also be about 100 ng-1 ug, about 1-3 μg, or about 3 to 20μg, for 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides. Although the sustained release amount of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides released each day can vary, a sustained release of 10 ng per day corresponds to about 0.4% of the 2.5 μg of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides applied with a single drop of a 0.005% solution.

For example, in the case of 17-phenyl trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides (compounds of formula IIb), synthetic prostamide prostaglandin analogues, the glaucoma medication may have concentrations that are 1/10,000th, 1/1000th, 1/500th, 1/100th, 1/50th, 2 percent, or 5%, that of bimatoprost. Therefore, the amount of drug loaded on the extended release device for a 3 to 6 month extended release, depending on the bioavailability, can be significantly

less, approximately 5-30 μg and typically 10- 20 μg - for bimatoprost and 1-10 μg and typically 100 ng to 1 μg for compounds of formula IIb, for example, 17-phenyl trinor $PGF_{2\alpha}$ isobutyl amides can have concentrations that are 1/200th less than that of bimatoprost. In many embodiments, the implant can house more drug for a longer sustained release period, for example, 20-40 μg for a sustained release period of 6 to 12 months with bimatoprost, however, 1-10 μg or 100 ng-1 μg with its hydrophobic ester or amide derivatives, for example, 17-phenyl trinor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides. This decrease in drug concentration can also translate to a device that can be smaller than one required for a beta blocker delivery.

Commercially available solution concentrations of bimatoprost are 0.03% by weight, often delivered once per day. Although the sustained release amount of bimatoprost released each day can vary, a sustained release of 300 ng per day corresponds to about 2 % of the 15 μg of bimatoprost applied with a single drop of a 0.03% solution.

Work in relation with the present disclosure indicates that even lower sustained release doses of compounds of formula IIb, for example, 17-phenyl trinor $PGF_{2\alpha}$ C_{4-32} esters or amides including 17-phenyl trinor $PGF_{2\alpha}$ isobutyl ester or amide can provide at least some reduction in intraocular pressure, for example, about 20 to about 200 ng of compounds of formula IIb and daily sustained release dosages of about 0.2 to about 2% of the daily drop dosage. In certain instances, about 4 ng to about 10 ng of compounds of formula IIb and daily sustained release dosage of about 0.04 to about 0.1% of the daily drop dosage can be achieved.

For example, in the case of 16-m-trifluoromethylphenoxy tetranor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides (compounds of formula IIc), prostaglandin F2α analogues, the glaucoma medication may have concentrations that are 1/10,000th, 1/1000th, 1/500th, 1/100th, 1/50th, or 2 percent, that of travoprost, for example, commercially available solution concentrations of travoprost are 0.004%, often delivered once per day. In many embodiments, the therapeutically effective concentration of drug released from the device per day can be about 10, 15, 20, 25, 30, 35, 40, 50, 55, 60, or 65 ng, assuming tear washout and bioavailability similar to travoprost. Therefore, the amount of drug on the implantable device,

depending on the bioavailability, would be significantly less. This also translates to a device that can either be smaller than one required for a beta blocker delivery or can house more drug for a longer release period, for example, the amount of drug on the implantable device, can be significantly less-approximately 1/100 of travoprost, for example, 30-100 ng, 100-300 ng, or 300 ng-130 μg as compared to 2.7 to 13.5 μg, and typically about 3 to 20μg, for travoprost. Using compounds IIc, as described herein, for example, 16-m-trifluoromethylphenoxy tetranor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides including isobutyl ester, the amount of drug on the implantable device can be 1/10000, 1/1000, 1/500 of travoprost. Although the sustained release amount of 16-m-trifluoromethylphenoxy tetranor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides released each day can vary, a sustained release of 10 ng per day corresponds to about 0.5% of the 2.0 μg of 16-m-trifluoromethylphenoxy tetranor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides applied with a single drop of a 0.004% solution. Because of its low solubility, which is easily tunable by adjusting the ester or amide functionalities, the compounds of formula IIc allow a sustained release of 10 ng per day, which corresponds to about 0.5% of the 2.0 μg of 16-m-trifluoromethylphenoxy tetranor $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides applied with a single drop of a 0.004% solution.

In some embodiments, the therapeutic agent may include a corticosteroid, for example, fluocinolone acetonide, to treat a target ocular tissue. In specific embodiments, fluocinolone acetonide can be released from the canaliculus and delivered to the retina as a treatment for diabetic macular edema (DME).

It is also within the scope of this invention to modify or adapt the devices to deliver a high release rate, a low release rate, a bolus release, a burst release, or combinations thereof. A bolus of the drug may be released by the formation of an erodible polymer cap that is immediately dissolved in the tear or tear film. As the polymer cap comes in contact with the tear or tear film, the solubility properties of the polymer enable the cap to erode and the drug is released all at once. A burst release of a drug can be performed using a polymer that also erodes in the tear or tear film based on the polymer solubility. In this example, the drug and polymer may be stratified along the length of the device so that as the outer polymer layer dissolves, the drug is immediately released. A high or

low release rate of the drug could be accomplished by changing the solubility of the erodible polymer layer so that the drug layer released quickly or slowly. Other methods to release the drug could be achieved through porous membranes, soluble gels (for example, those in typical ophthalmic solutions), microparticle encapsulations of the drug, or nanoparticle encapsulation, depending on the size of the drug molecule.

Release of Therapeutic Agent at Effective Levels

The rate of release of the therapeutic agent can be related to the concentration of therapeutic agent dissolved in the drug core. In many embodiments, the drug core includes non-therapeutic agents that are selected to provide a desired solubility of the therapeutic agent in the drug core. The non-therapeutic agent of the drug core can include polymers as described herein, and additives. A polymer of the core can be selected to provide the desired solubility of the therapeutic agent in the matrix, for example, the core can include hydrogel that may promote solubility of hydrophilic treatment agent. In some embodiments, functional groups can be added to the polymer to provide the desired solubility of the therapeutic agent in the matrix, for example, functional groups can be attached to silicone polymer.

In some embodiments, additives may be used to control the release kinetics of therapeutic agent, for example, the additives may be used to control the concentration of therapeutic agent by increasing or decreasing solubility of the therapeutic agent in the drug core so as to control the release kinetics of the therapeutic agent. The solubility may be controlled by providing appropriate molecules and/or substances that increase and/or decrease the solubility of the dissolved from of the therapeutic agent to the matrix. The solubility of the dissolved from the therapeutic agent may be related to the hydrophobic and/or hydrophilic properties of the matrix and therapeutic agent, for example, surfactants, salts and water can be added to the matrix and may increase the solubility of hydrophilic therapeutic agent in the matrix. In addition, oils and hydrophobic molecules and can be added to the matrix and may increase the solubility of hydrophobic treatment agent in the matrix.

Instead of or in addition to controlling the rate of migration based on the concentration of therapeutic agent dissolved in the matrix, the surface area of the

drug core can also be controlled to attain the desired rate of drug migration from the core to the target site, for example, a larger exposed surface area of the core will increase the rate of migration of the treatment agent from the drug core to the target site, and a smaller exposed surface area of the drug core will decrease the rate of migration of the therapeutic agent from the drug core to the target site. The exposed surface area of the drug core can be increased in any number of ways, for example, by any of castellation of the exposed surface, a porous surface having exposed channels connected with the tear or tear film, indentation of the exposed surface, protrusion of the exposed surface. The exposed surface can be made porous by the addition of salts that dissolve and leave a porous cavity once the salt dissolves. Hydrogels may also be used, and can swell in size to provide a larger exposed surface area. Such hydrogels can also be made porous to further increase the rate of migration of the therapeutic agent.

Further, an implant may be used that includes the ability to release two or more drugs in combination, for example, the structure disclosed in U.S. Patent No. 4,281,654 (Shell), for example, in the case of glaucoma treatment, it may be desirable to treat a patient with multiple prostaglandins or a prostaglandin and a cholinergic agent or an adrenergic antagonist (beta blocker), for example, Alphagan (Allegan, Irvine, CA, USA), or a prostaglandin and a carbonic anhydrase inhibitor.

In addition, drug impregnated meshes may be used, for example, those disclosed in U.S. Patent Application Publication No. 2002/0055701 or layering of biostable polymers as described in U.S. Patent Application Publication No. 2005/0129731. Certain polymer processes may be used to incorporate drug into the devices, as described herein, for example, so-called "self-delivering drugs" or PolymerDrugs (Polymerix Corporation, Piscataway, NJ, USA) are designed to degrade only into therapeutically useful compounds and physiologically inert linker molecules, further detailed in U.S. Patent Application Publication No. 2005/0048121 (East), hereby incorporated by reference in its entirety. Such delivery polymers may be employed in the devices, as described herein, to provide a release rate that is equal to the rate of polymer erosion and degradation and is constant throughout the course of therapy. Such delivery polymers may be used as device coatings or in the form of microspheres for a drug depot injectable (for example, a reservoir described herein). A further polymer

delivery technology may also be adapted to the devices, as described herein, for example, that described in U.S. Patent Application Publication No. 2004/0170685 (Carpenter), and technologies available from Medivas (San Diego, CA, USA).

In many embodiments, the therapeutic agent has a very low solubility in water, for example, from about 0.03% by weight to about 0.0001 % by weight, a molecular weight from about 400 grams per mole (g/mol.) to about 1200 g/mol, and is readily soluble in an organic solvent. Cyclosporin A (CsA) is a solid with an aqueous solubility of 27.67 μg/mL at 25 °C, or about 0.0027% by weight, and a molecular weight (M.W.) of 1202.6 g/mol. Latanoprost (Xalatan) is a prostaglandin F2α analogue, a liquid oil at room temperature, and has an aqueous solubility of 50 μg/mL in water at 25 °C, or about 0.005% by weight and a M.W. of 432.6 g/mol. Bimatoprost (Lumigan) is a synthetic prostamide analogue, a solid at room temperature solubility in water of 300 μg/mL in water at 25 °C, or 0.03% by weight, and has a M.W. of 415.6 g/mol.

Work in relation with the present disclosure indicates that naturally occurring surfactants in the tear film, for example, surfactant D and phospholipids, may effect transport of the drug dissolved in the solid matrix from the core to the tear film. The drug core can be adapted in response to the surfactant in the tear film to provide sustained delivery of the drug into the tear film at therapeutic levels, for example, empirical data can be generated from a patient population, for example, 10 patients whose tears are collected and analyzed for surfactant content. Elution profiles in the collected tears for a drug that is sparingly soluble in water, for example, cyclosporine, can also be measured and compared with elution profiles in buffer and surfactant such that an *in vitro* model of tear surfactant is developed. An *in vitro* solution with surfactant based on this empirical data can be used to adjust the drug core in response to the surfactant of the tear film.

In many embodiments, the drug insert includes of a thin-walled polyimide tube sheath with a drug core including compounds of formula I or II, for example, compounds IIa, dispersed in Nusil 6385 (MAF 970), a medical grade solid silicone that serves as the matrix for drug delivery. The distal end of the drug insert is sealed with a cured film of solid Loctite 4305 medical grade adhesive. The drug insert may be placed within the bore of the punctum plug,

the Loctite 4305 adhesive does not come into contact with either tissue or the tear film. The inner diameter of the drug insert can be 0.32 mm; and the length can be 0.95 mm. Three concentrations in the finished drug product can be tested clinically: Drug cores can include 3.5, 7, or 14 μg isobutyl ester of Latanoprost, with per cent by weight concentrations of 5, 10 and 20% respectively. Assuming an overall elution rate of approximately 100 ng/day, the drug core including 14 μg of prodrug is adapted to deliver drug for approximately at least 100 days, for example, 120 days. The overall weight of the drug core, including prodrug, can be approximately 70 μg. The weight of the drug insert including the polyimide sleeve can be approximately 100 μg.

In many embodiments, the drug core may elute with an initial elevated level of therapeutic agent followed by substantially constant elution of the therapeutic agent. An elevated level of eluted therapeutic agent can result in a residual amount of therapeutic agent and/or residual effect of the therapeutic agent that is combined with a therapeutic amount of therapeutic agent to provide relief to the patient. In embodiments where therapeutic level is about 80 ng per day, the device may deliver about 100 ng per day for an initial delivery period. The extra 20 ng delivered per day can have a beneficial effect. As the amount of drug delivered can be precisely controlled, an initial elevated dose may not result in complications and/or adverse events to the patient.

Concentrations, amounts, etc., of various components are often presented in a range format throughout this disclosure. The description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the claimed invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range, for example, description of a range, for example, 1% to 8% should be considered to have specifically disclosed sub-ranges, for example, 1% to 7%, 2% to 8%, 2% to 6%, 3% to 6%, 4% to 8%, 3% to 8% etc., as well as individual numbers within that range, for example, 2%, 5%, 7% etc. This construction applies regardless of the breadth of the range and in all contexts throughout this disclosure.

In the claims provided herein, the steps specified to be taken in a claimed method or process may be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is

explicitly defined by claim language. Recitation in a claim to the effect that first a step is performed then several other steps are performed shall be taken to mean that the first step is performed before any of the other steps, but the other steps may be performed in any sequence unless a sequence is further specified within the other steps, for example, claim elements that recite "first A, then B, C, and D, and lastly E" shall be construed to mean step A must be first, step E must be last, but steps B, C, and D may be carried out in any sequence between steps A and E and the process of that sequence will still fall within the four corners of the claim.

Furthermore, in the claims provided herein, specified steps may be carried out concurrently unless explicit claim language requires that they be carried out separately or as parts of different processing operations, for example, a claimed step of doing X and a claimed step of doing Y may be conducted simultaneously within a single operation, and the resulting process will be covered by the claim. Thus, a step of doing X, a step of doing Y, and a step of doing Z may be conducted simultaneously within a single process step, or in two separate process steps, or in three separate process steps, and that process will still fall within the four corners of a claim that recites those three steps.

Similarly, except as explicitly required by claim language, a single substance or component may meet more than a single functional requirement, provided that the single substance fulfills the more than one functional requirement as specified by claim language.

Examples

Example 1

Preparation of 17-phenyl-13,14-dihydrotrinor Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) isobutyl ester

To a round bottom flask equipped with a magnetic stirring bar is charged with 19.5 mg (0.05 mmol.) 17-phenyl-13,14-dihydro trinor $PGF2_{\alpha}$ (Cayman Chemical Company, Ann Arbor, MI,USA), 5 ml CH_2Cl_2, 30.2 mg (0.23 mmol.) diisopropylethylamine. This solution is stirred at a temperature from 0-10 °C and 13.5 mg (0.07 mmol.) of isobutyltriflate is added. This solution is allowed to stand at between 0-10 °C for 15 min and is slowly warmed to room

temperature. When the esterification is complete according to TLC (usually after 3-4 h at room temperature) the solvent is removed *in vacuo*. The residue is diluted with 20 ml ethyl acetate, washed with 2 X 10 ml 5% sodium hydrogen carbonate and 2 X 10 ml 3% citric acid. The organic layer is dried over anhydrous sodium sulfate. The solvent is removed *in vacuo* and the residue is purified by flash column chromatography on silica gel using ethyl acetate: acetone as eluent. The compound is obtained as a colorless oil.

Example 2

Preparation of (+)-16-m-trifluoromethylphenoxy tetranor ($PGF_{2\alpha}$) isobutyl ester

To a round bottom flask equipped with a magnetic stirring bar is charged with 23 mg (0.05 mmol.) (+)-16-m-trifluoromethylphenoxy tetranor Prostaglandin $F_{2\alpha}$ (Cayman Chemical Company, Ann Arbor, MI,USA), 6 ml acetone, 39.2 mg (0.25 mmol.) DBU and 42.5 mg (0.25 mmol.) isobutyl iodide. The solution is allowed to stand at room temperature for 24 h, the solvent is removed *in vacuo* and the residue is diluted with 30 ml of ethyl acetate, washed twice with 10 ml 5% sodium bicarbonate and 10 ml 3% citric acid. The solvent is removed *in vacuo*, and the crude product is purified by flash chromatography on silica gel using ethyl acetate: acetone as eluent. The compound is obtained as an oil.

Example 3

Hydrolysis of 17-phenyl-13,14-dihydro trinor Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) isopropyl ester

17-phenyl-13,14-dihydro trinor Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) isopropyl ester (43 mg, 0.1 mmol.) is diluted with THF (1.0 mL) and lithium hydroxide (0.4 mL of a 0.5 N solution in H_20, 0.2 mmol.) is added. After 16 h the reaction is acidified with 1N HCl and extracted with EtOAc. The organic portion is washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ (> 90% yield).

Example 4

Preparation of 17-phenyl trinor $PGF_{2\alpha}$ isobutyl amide from ester

A solution of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ isopropyl ester (43.3 mg, 0.1 mmol.) and isobutylamine (1.0 mL, 10.1 mmol.) in MeOH (4.0 mL) is heated to 80 °C for 24-48 hours. The reaction is cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH as eluent to afford 17-phenyl trinor $PGF_{2\alpha}$ isobutyl amide (> 80% yield).

Example 5

Preparation of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ isobutyl amide from acid

To a flask equipped with a magnetic stir-bar is added a solution of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ (39.1 mg, 0.1 mmol.) and isobutylamine (12 μL, 0.12 mmol.) in THF (1.0 mL) under an argon atmosphere. After cooling to 0 °C with the aid of an ice-water bath, a solution of DCC (24.8 mg, 0.12 mmol.) in THF (1.0 ml) is added and the reaction mixture is allowed to warm to room temperature while stirring overnight. The mixture is filtered through CELITE, concentrated, and purified by column chromatography using ethyl acetate/hexane as eluent to afford 17-phenyl trinor $PGF_{2\alpha}$ isobutyl amide (> 70% yield).

Example 6

Studies of eye pressure lowering effect

The intraocular pressure (IOP) is determined in animals with a pneumatonometer (Digilab Modular One, Bio Rad, Cambridge, MA, USA), specially calibrated for the eye of the particular species. The cornea is anaesthetized with 1-2 drops of oxibuprocain before each XOP measurement. In healthy human volunteers IOP is measured with applanation tonometry or with an air puff tonometer (Keeler pulsair). For applanation tonometry either a pneumatonometer (Digilab) or Goldmann's applanation tonometer mounted on a slit lamp microscope is used. The cornea is anaesthetized with oxibuprocain before each measurement with applanation tonometry. No local anesthesia is employed before measurement with the pulsair tonometer.

Example 7

Comparison studies of eye pressure lowering effect of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ esters and amides with latanoprost

This Example illustrates an IOP test using the monkey eye in which about one tenth the clinical dose of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ ester or amide is compared in IOP reduction with the same dose of latanoprost. The intraocular pressure lowering effects of the 0.0005% solution of 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ isobutyl ester and the 0.0005% solution of 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester (latanoprost) are compared following a single, topical ocular instillation in monkeys.

Preparation of Dosing Solutions:

A solution containing 17-phenyl-13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ isobutyl ester or latanoprost at 0.0005% is prepared with the following vehicle. Composition of the vehicle (/mL): NaCl (4.1 mg), NaH_2PO_4-H_2O (4.6 mg), Na_2HPO_4-$2H_2O$ (5.94 mg), Benzalkonium Chloride (0.2 mg) and water for injection.

Animals:

Five male cynomolgus monkeys (Kasyo Co., Ltd., Tokyo, Japan) are used. These monkeys are housed individually in cages for monkeys in a room, which is maintained at room temperature of 24±1 °C, relative humidity of 55±10%, ventilation rate of about 12 times/hour and 12-hour light-dark cycle (fluorescent lighting: 8:00 a.m. to 8:00 p.m.). The animals are given food pellets for monkeys (PS, Oriental Yeast Co., Ltd., Tokyo, Japan), vegetables and fruits, and allowed free access to tap water from an automatic dispenser. The healthy animals without abnormalities in the anterior segment of the eye are used in this study.

Test Groups and Administration Method:

Group	Administration Method	Volume of Administration	N
17-phenyl- 13,14-dihydro trinor $PGF_{2\alpha}$ isobutyl ester 0.0005%	Instillation	35 μL/eye	5
latanoprost 0.005%	Instillation	35 μL/eye	5

Five monkeys are divided into 2 groups of the group 1 (3 monkeys) and group 2 (2 monkeys). The 0.0005% 17-phenyl-13,14-dihydro trinor $PGF_{2\alpha}$ isobutyl ester and 0.0005% latanoprost are instilled into the right eye of monkeys in the group 1 and 2, respectively. One week later, 0.0005% latanoprost and 0.0005% 15-keto-latanoprost are instilled into the right eye of monkeys in the group 1 and 2, respectively, in a crossover way. Thirty-five μL of each test solution is administered by use of a micropipette (Pipetman P 100, Gilson). To the left eye the same volume of the vehicle was administered. The intraocular pressure in each group before the instillation is measured (in mmHg, mean.+-.S .E.).

Measurement of Intraocular Pressure:

The animals are systemically anesthetized by an intramuscular injection of 5 mg/kg of ketamine hydrochloride (Ketalar 50, Sankyo Co., Ltd., Tokyo, Japan), and the anterior segment of both eyes is anesthetized by a instillation of 0.4% oxybuprocaine hydrochloride (Benoxil 0.4% solution, Santen Pharmaceutical Co., Ltd., Tokyo, Japan). The animals are fixed in a sitting position, and the intraocular pressure is measured by use of an applanation pneumatonograph (Alcon Japan Ltd.) before, and 2, 4, 8, 12 and 24 hours after the instillation. The animals are kept in cages excepting the time of measurement of the intraocular pressure. The data are statistically analyzed with Student's t-test. P values less than 0.05 are considered to be statistically significant.

Example 8

Evaluation of Ocular Irritation

Thirty albino rabbits are randomly divided into five groups. Each rabbit is dosed in the conjunctival sac of the right eye topically every ten minutes for one hour (six doses) with 50 μL of 0.0%, 0.396, 0.5%, 1.0% and 2% of test compound, in 0.9% saline solution. The treated eye of each rabbit is examined for indications of ocular irritation, including swelling, discharge, redness, iritis of conjunctiva, eyelid, iris as well as opacity and involvement of the cornea. Individual scores are added to determine the degree of slight, moderate, or severe irritation. Ocular observations were made before the treatment, one hour after the first and sixth instillation and then 1, 2, 3, 4 and 7 days, using a slit lamp.

Example 9

Corneal Anesthesia Measurements

The effect of a 50 μL single instillation of 0.3%, 0.5%, 1.0% and 2.0% solution of $PGF_{2\alpha}$ ester or amide prodrug on corneal anesthesia, after a single instillation in the conjunctival sac of the right eyes of albino rabbits (N=5) is measured using a Cochet's esthesiometer (nylon thread: 0.12 mm diameter, 10 mm long). Corneal anesthesia is evaluated by the number of comeal mechanical stimuli necessary to induce a blinking reflex. The effect of drug solutions is compared with sterile 0.9% NaCl treated animals (control group) and 0.4% oxybuprocaine (e.g., Novesine).

Example 10

Stability Tests

An accelerated stability test is conducted on 0.25% solutions of $PGF_{2\alpha}$ isobutyl ester or amide at 40 °C for 1, 2, 3, 4, 8, and 12 weeks and is monitored for the disappearance of the prodrugs and appearance of the parent compound by HPLC analysis.

The respective compounds are dissolved in an acetate buffer, pH 3.5 (0.018% sodium acetate, 0.135% acetic acid, 0.9% sodium chloride in water for injection) to obtain 0.25% solution. The stability of the compounds is determined at 40 °C for 1, 2, 3, 4, 8, and 12 weeks. The concentration of the

parent compound as well as the concentrations of the prodrug compounds 6, 7, and 8 at each time point are determined by HPLC method.

Example 11

Measurement of Octanol-Water Partition Coefficient

Test Method

$PGF_{2\alpha}$ $C_{4\text{-}32}$ alkyl esters or amides are dissolved in 10 mM sodium dihydrogenphosphate dehydrate buffer (pH 7.8) in such a manner that said esters or amides become to be 0.1 weight/volume (w/v) % of this solution and 5 mL of water-saturated octanol are poured into 20 mL of a glass ampoule. The ampoule is sealed and shaken at 100 rpm and 25 °C for 18 hours. After shaking, the glass ampoule was allowed to stand at room temperature. The octanol phase (upper phase) and the aqueous phase (lower phase) are taken into glass tubes respectively, using a Pasteur pipette. Each of the phase taken is centrifuged for 10 minutes at 2000 rpm to separate the octanol phase and the aqueous phase completely. Each 1 mL of the separated octanol phase and aqueous phase is diluted with a diluent solvent (water/acetonitrile =50/50 volume/volume (v/v)) to a precise volume of 50 mL, and served as a sample for HPLC. The concentration of $PGF_{2\alpha}$ $C_{4\text{-}32}$ alkyl esters or amides in each phase is determined by high performance liquid chromatography (Shimadzu Co., type:LC-10AD; Detector: Ultraviolet spectrophotometer (wave length for measurement: 266 nm; Column: A column packed with 5 μm of octadecylsilyl silica gel for liquid chromatography, wherein the column is a stainless tube having about 4.6 mm of inner diameter and about 25 cm of length. (CAPCELL PAK C18, SG120 5 μm, 4.6 mm I.D. X 250 mm, Shiseido Co., Ltd., Tokyo, Japan); Guard column: ODS 80TS (TOSOH Co., Tokyo, Japan); Column temperature: a constant temperature of about 40 °C; Mobile phase: 1.98 g of diammonium hydrogenphosphate was dissolved in 750 mL of water. Phosphoric acid was added thereto to adjust the pH to 7.3, and 250 mL of acetonitrile was mixed therewith; Flow rate: 1.1 mL/min. Injection amount: 10 μL). As a control, there was used a solution of only latanoprost dissolved in 10 mM NaH_2PO_4 dihydrate buffer (pH 7.8) so as to be 0.1 w/v %.

Calculation of Octanol-Water Partition Coefficient

The octanol-water partition coefficient (P) is calculated by the following equation. Octanol-water partition coefficient = (Concentration of $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides in the octanol phase)/(Concentration of $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides in the aqueous phase). LogP is defined as the logarithm of the ratio of the concentrations of solute in octanol and water.

Latanoprost has a logP value of 4.027 at a pH about 7.4. Bimatoprost has a logP value of 2.4 at a pH about 7.4. Travoprost has a logP value of 3.725 at a pH about 7.4. The $PGF_{2\alpha}$ C_{4-32} alkyl esters and amides, as described herein, have logPs greater than 2.4 at a pH about 7.4.

Example 12

Penetration Test into the Aqueous Humor

Penetration tests of $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides into the aqueous humor and latanoprost are carried out as follows.

Albino rabbits, which have no abnormal cornea are selected (n=5), and 1.5 μL of each test material (eye drops of Formulations 1 to 3) is administered once to the rabbits by using a pipette. The rabbits are euthanized by overdosing a solution of pentbarbital sodium 2 hours after the intraocular administration. After the external segment of the eye is washed with physiological saline, the aqueous humor is collected by using a syringe with a 27G injection needle. 160 μL of the collected aqueous humor is mixed with 160 μL of a mobile phase for pretreatment/concentration as mentioned below, and the mixture was filtered with a membrane filter (0.45 μm). The filtrate is served as a sample of HPLC measurement and the concentration of free acid is determined using High Performance Liquid Chromatograph.

One eye drop typically contains 1.5 μg of prodrugs, for example, the $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides. The eye drop is administered at 0.5, 1, 2, 4 and 24 hours and are studied in three groups of 20 rabbits. The mean concentration at about 0.5, 1, 2, 4 and 24 hours after topical administration of prodrug is measured relative to latanoprost is measured. The mean concentration at around 0.5, 1, 2, 4 and 24 hours after topical administration of latanoprost are 5.7, 18.7, 32.6, 29.0 and 0.2 ng/ml, respectively. Typically, the

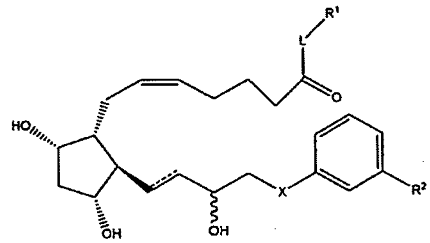
maximum concentration of the free acid of latanoprost in aqueous humor is 33-34 ng/ml obtained 2.5 h after topical administration of 1.5 μg latanoprost to the eye. The maximum concentration of the acid of latanoprost in aqueous humor is from 30-50 ng/ml obtained 2.5 h after topical administration of 1.5 μg $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides to the eye. As demonstrated, the penetration of $PGF_{2\alpha}$ C_{4-32} alkyl esters or amides into the aqueous humor is significantly increased as compared to latanoprost.

While the exemplary embodiments have been described in some detail, by way of example and for clarity of understanding, those of skill in the art will recognize that a variety of modification, adaptations, and changes may be employed, for example, multiple delivery mechanisms may be employed, and each device embodiment may be adapted to include features or materials of the other, and further multiple features or multiple materials may be employed in a single device. Hence, the scope of the present invention may be limited solely by the appending claims.

All patents, patent applications, publications, scientific articles, web sites, and other documents and materials referenced or mentioned herein are indicative of the levels of skill of those skilled in the art to which the invention pertains, and each such referenced document and material is hereby incorporated by reference to the same extent as if it had been incorporated by reference in its entirety individually or set forth herein in its entirety. Additionally, all claims in this application, and all priority applications, including but not limited to original claims, are hereby incorporated in their entirety into, and form a part of, the written description of the invention. Applicants reserve the right to physically incorporate into this specification any and all materials and information from any such patents, applications, publications, scientific articles, web sites, electronically available information, and other referenced materials or documents. Applicants reserve the right to physically incorporate into any part of this document, including any part of the written description, the claims referred to above including but not limited to any original claims.

What is claimed is:

1. A compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

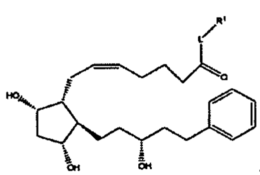
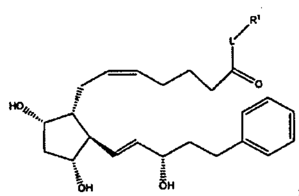
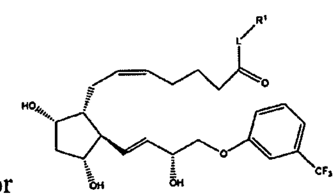
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

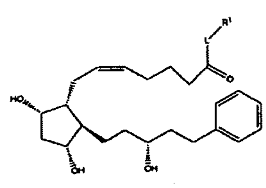
2. A compound of claim 1, wherein the compound of formula II is

, , or 

IIa IIb IIc,

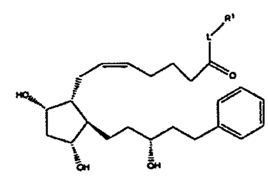
wherein L is -O- or is -NH- and R^1 is isobutyl.

3. A compound of claim 2, wherein the compound of the formula II is:



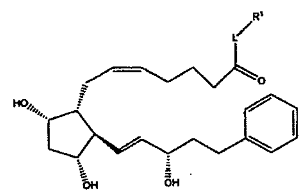
IIa,

wherein L is –O- and R^1 is isobutyl;



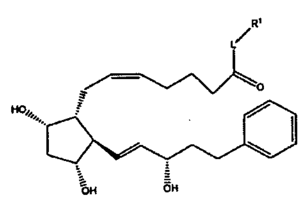
IIa,

wherein L is –NH- and R^1 is isobutyl;



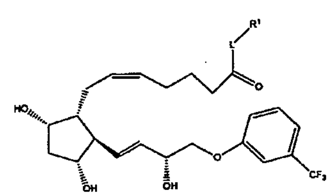
IIb,

wherein L is –O- and R^1 is isobutyl;



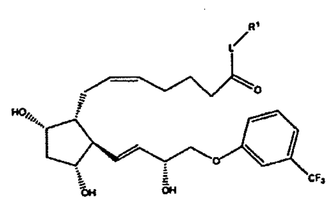
IIb,

wherein L is –NH- and R^1 is isobutyl;



IIc,

wherein L is –O- and R^1 is isobutyl; or



IIc,

wherein L is –NH- and R^1 is isobutyl.

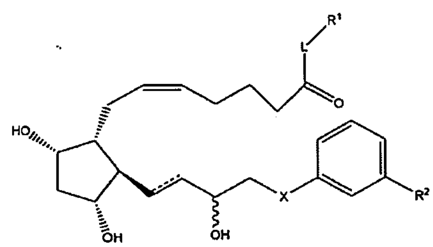
4. A compound of claim 1 having a water solubility from about 4 ng/ml to about 16 mg/ml or a logP from about 2.5 to about 9.0 at a pH of about 7.

5. A compound of claim 1, which is present in an aqueous humor as a free acid at about 0.5 hours after topical administration in a mean concentration greater than about 5.7 ng/ml, or at about 1 hour after topical administration to an eye in a mean concentration greater than about 18.7 ng/ml, or at about 2 hours after topical administration in a mean concentration greater than about 32.6 ng/ml, or at about 4 hours after topical administration in a mean concentration greater than about 29.0 ng/ml, or at about 24 hours after topical administration in a mean concentration greater than about 0.2 ng/ml, or a combination thereof.

6. A compound of claim 1, which is hydrolysable by an esterase.

7. A composition comprising:

a compound of formula II:



II

wherein:

L is -O- or $-NR^a-$, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or $-CH_2-$;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and

a pharmaceutically acceptable carrier.

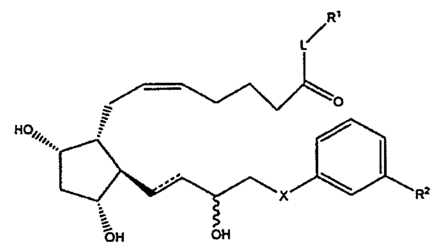
8. A composition of claim 7, for use in treating an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair.

9. A composition of claim 8, wherein the eye disease is glaucoma.

10. A composition of claim 7, wherein the pharmaceutically acceptable carrier comprises a silicone matrix.

11. A method of treating glaucoma in a subject in need thereof comprising administering to the subject an effective amount of a composition comprising:

a compound of formula II:



II

wherein:

L is -O- or $-NR^a-$, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or $-CH_2-$;

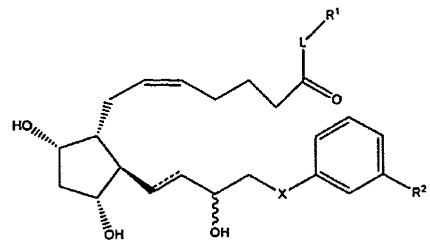
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4; and

an optional pharmaceutically acceptable carrier.

12. A method of claim 11, wherein the composition is administered to an eye of the subject.

13. A method of delivering a therapeutic agent to an eye having associated tears comprising: administering the therapeutic agent to the eye in need thereof through operation of a drug core containing the therapeutic agent, wherein the therapeutic agent comprises a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4.

14. The method of claim 13, wherein the administering further comprises:

contacting the drug core with the eye; and

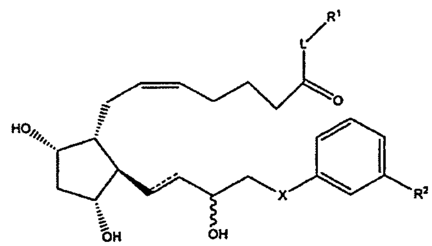
releasing the therapeutic agent to the tears of the eye.

15. The method of claim 13, wherein the therapeutic agent and a silicone matrix form the drug core.

16. The method of claim 15, wherein the drug core is placed in a canaliculus of the eye.

17. The method of claim 13, wherein the therapeutic agent dissolves into the silicone matrix and the silicone matrix remains saturated with the therapeutic agent.

18. A compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

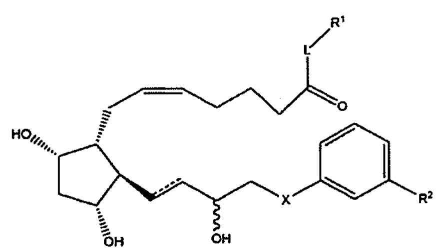
----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, for use in medical therapy.

19. The use of claim 18, wherein the medical therapy is the treatment of an eye disorder, an eye disease, or the cosmetic enhancement of eyelash hair or eyebrow hair.

20. The use of claim 19, wherein the eye disease is glaucoma.

21. Use of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

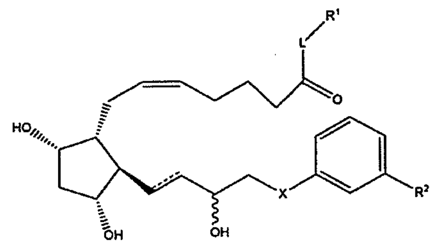
R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, to prepare a medicament for treatment of glaucoma.

22. A method of increasing length, thickness, number, or density, of eyelash hair or eyebrow hair, comprising administering an effective amount of a compound of formula II:



II

wherein:

L is -O- or -NR^a-, wherein R^a is -H or C_1-C_8 alkyl;

R^1 is C_{4-32} alkyl;

R^2 is -H or C_1-C_8 haloalkyl;

X is -O- or -CH_2-;

----- represents an optional double bond; or a pharmaceutically acceptable salt, a metabolite, or a prodrug thereof,

wherein the compound of formula II has a water solubility of no more than about 16 mg/ml or a logP greater than about 2.4 at a pH of about 7.4, to a person on the area where hair growth is desired.

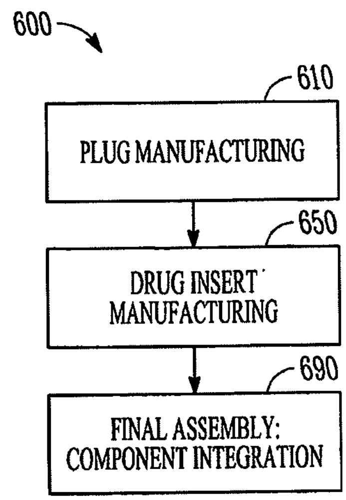

600
610
PLUG MANUFACTURING
650
DRUG INSERT MANUFACTURING
690
FINAL ASSEMBLY: COMPONENT INTEGRATION

FIG. 1

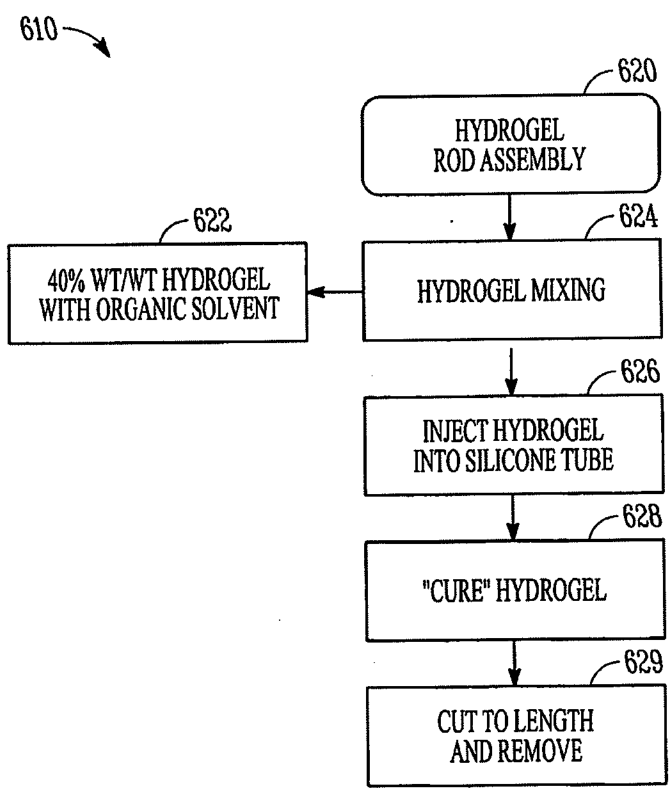

610
620
HYDROGEL ROD ASSEMBLY
622
40% WT/WT HYDROGEL WITH ORGANIC SOLVENT
624
HYDROGEL MIXING
626
INJECT HYDROGEL INTO SILICONE TUBE
628
"CURE" HYDROGEL
629
CUT TO LENGTH AND REMOVE

FIG. 2

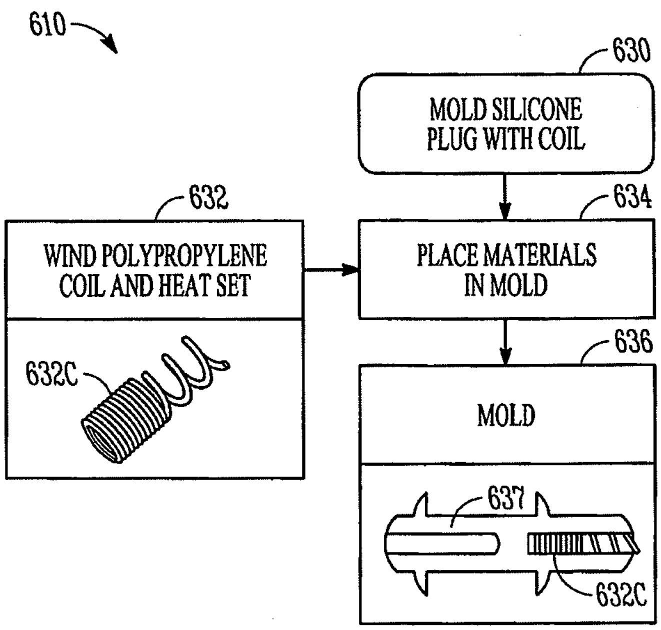

610
630
MOLD SILICONE PLUG WITH COIL
632
WIND POLYPROPYLENE COIL AND HEAT SET
634
PLACE MATERIALS IN MOLD
632C
636
MOLD
637
632C

FIG. 3

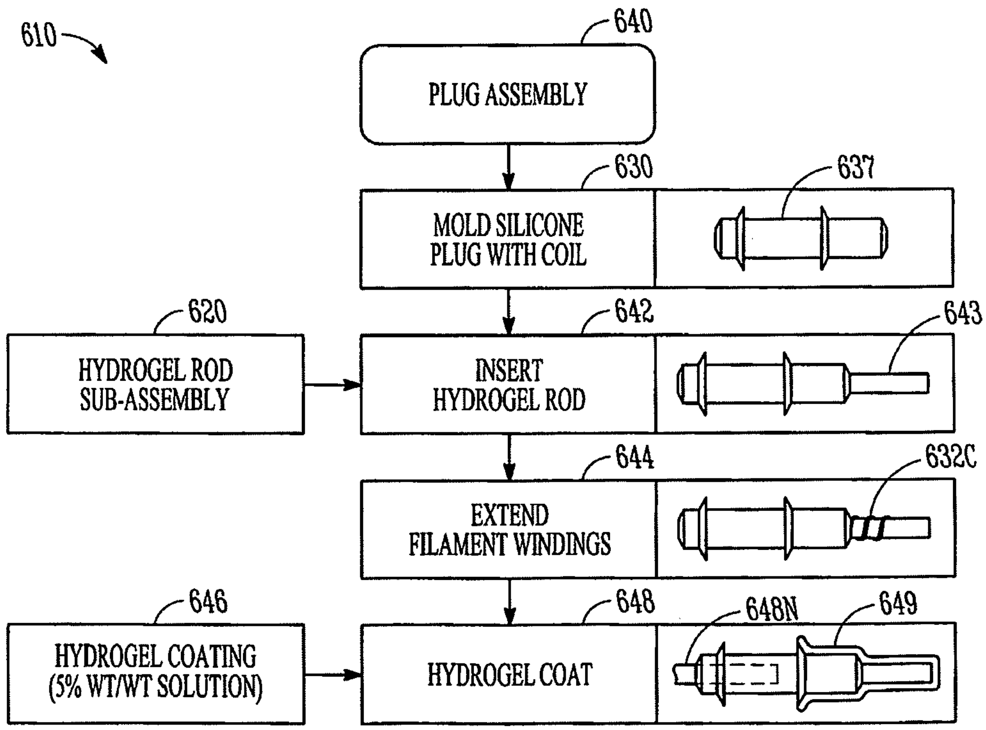

610
640
PLUG ASSEMBLY
630
MOLD SILICONE PLUG WITH COIL
637
620
HYDROGEL ROD SUB-ASSEMBLY
642
INSERT HYDROGEL ROD
643
644
EXTEND FILAMENT WINDINGS
632C
646
HYDROGEL COATING (5% WT/WT SOLUTION)
648
HYDROGEL COAT
648N
649

FIG. 4

3/3

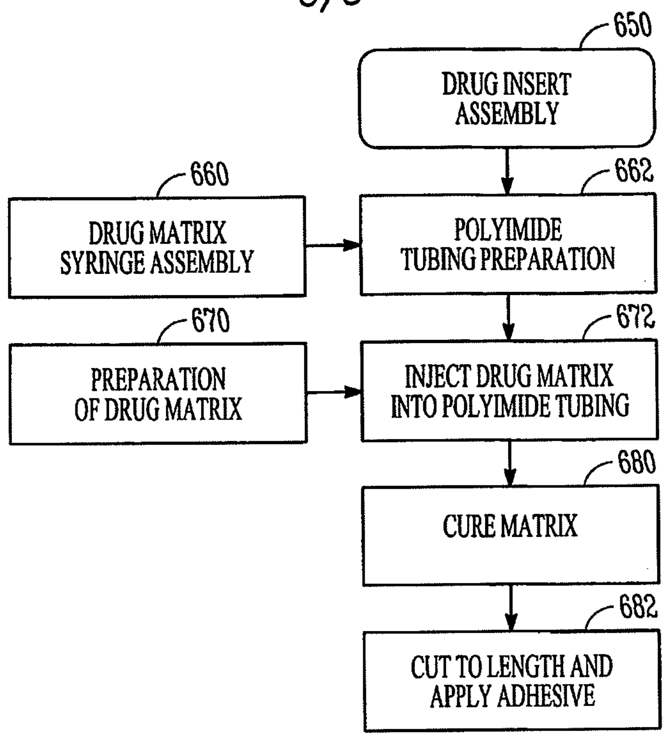

650
DRUG INSERT ASSEMBLY
660
DRUG MATRIX SYRINGE ASSEMBLY
662
POLYIMIDE TUBING PREPARATION
670
PREPARATION OF DRUG MATRIX
672
INJECT DRUG MATRIX INTO POLYIMIDE TUBING
680
CURE MATRIX
682
CUT TO LENGTH AND APPLY ADHESIVE

FIG. 5

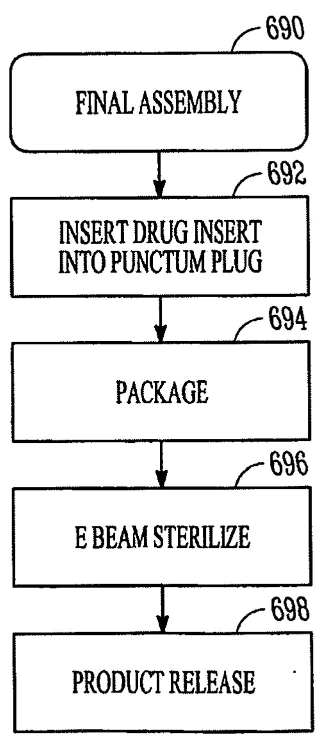

690
FINAL ASSEMBLY
692
INSERT DRUG INSERT INTO PUNCTUM PLUG
694
PACKAGE
696
E BEAM STERILIZE
698
PRODUCT RELEASE

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/010494

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C405/00 A61K31/5575 A61P9/10 A61Q5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K A61P A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2007/127639 A (AERIE PHARMACEUTICALS INC [US]; DELONG MITCHELL A [US]; MCFADDEN JILL) 8 November 2007 (2007-11-08)	1,7-22
A,P	page 53; examples 20-23,28-31 page 55; examples 78,80,82-84,86,87 page 56; examples 101-104 page 70, paragraph 241 - page 72, paragraph 251	2-8
X	WO 2005/068421 A (NICOX SA [FR]; ONGINI ENNIO [IT]; BENEDINI FRANCESCA [IT]; CHIROLI VAL) 28 July 2005 (2005-07-28) the whole document	1-22

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2009	13/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bedel, Christian

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/010494

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACEK G. MARTYNOW ET AL: "A New Synthetic Approach to High-Purity (15R)-Latanoprost" EUR. J. ORG. CHEM., 2007, pages 689-703, XP002512430 cited in the application page 694; figure 53; example 25	1
A	RESUL B ET AL: "PHENYL-SUBSTITUTED PROSTAGLANDINS: POTENT AND SELECTIVE ANTIGLAUCOMA AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, US AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 36, no. 2, 1 January 1993 (1993-01-01), pages 243-248, XP000673914 ISSN: 0022-2623 the whole document	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/010494

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007127639 A	08-11-2007	US 2007254920 A1	01-11-2007
WO 2005068421 A	28-07-2005	AR 047081 A1	04-01-2006
		AU 2004313688 A1	28-07-2005
		BR PI0418245 A	17-04-2007
		CA 2551409 A1	28-07-2005
		CN 1906159 A	31-01-2007
		EP 1704141 A1	27-09-2006
		JP 3984283 B2	03-10-2007
		JP 2007518716 T	12-07-2007
		KR 20060113753 A	02-11-2006
		KR 20080007415 A	18-01-2008
		MX PA06007678 A	01-09-2006
		PA 8620901 A1	30-08-2005
		US 2005272743 A1	08-12-2005
		US 2008058392 A1	06-03-2008
		UY 28709 A1	31-08-2005